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THE EFFECT OF THEOPHYLLIN WITH ETHYLENEDIAMINE (AMINOPHYLLINE) AND OF PAPAVERINE HYDROCHLORIDE ON EXPERIMENTAL MYOCARDIAL INFARCTION IN THE DOG

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AMINOPHYLLINE has been widely used in coronary disease as a coronary dilator because this effect has been demonstrated in the experimental animal. However, the evidence in regard to its clinical efficacy has been conflicting. Boyer,[1] in a critical review of therapeutic claims for aminophylline and related xanthine derivatives concludes that the evidence pro and con is still inconclusive.

Papaverine has been found to be a powerful and long-lasting coronary vasodilator,[2] much more effective than aminophylline. Clinically, we have found that it has a beneficial effect in angina pectoris,[3] and this clinical impression has been confirmed by others.

Both aminophylline and papaverine have been used during acute myocardial infarction not only to alleviate pain, but with the hope that the infarct healing would be accelerated and the infarct minimized.

The evidence supporting this use of the drugs is controversial in the case of aminophylline as far as experimental myocardial infarction is concerned, and no data on the effect of papaverine in experimental myocardial infarction have been obtained. In the case of aminophylline, Gold, Travell, and Modell,[4] working with cats, found that when therapeutic doses (about one and one-half times those recommended in man) are given intramuscularly for three weeks after ligation of the circumflex branch of the left coronary artery, the size of the infarct is not reduced, as was revealed by comparison with untreated controls. However, Fowler, Hurevitz, and Smith[5] concluded that the infarct size in dogs following ligation of the left anterior descending coronary artery is reduced, compared with that in untreated animals, in animals treated for three weeks with aminophylline (0.2 Gm. daily by mouth, a dosage roughly equivalent to that used in man).

The present study was undertaken because of the absence of data on papaverine and the controversy concerning the efficacy of aminophylline on myo-

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cardial infarct size. The influence of these two drugs was compared by measuring the size of the myocardial infarcts eight weeks after ligation of the left anterior descending coronary artery in untreated dogs and dogs treated during this period with either aminophylline or papaverine.

It has been shown by Gregg, Thornton, and Mautz,[6] in chronic coronary occlusion experiments, that over the course of days to weeks the retrograde flow of blood in the occluded artery increases and tends eventually to approximate the pre-occlusion inflow rate. This increasing retrograde flow leads to noticeable augmentation of peripheral coronary pressure in the occluded vessel below the occlusion and to a return of contraction in the ischemic yet viable areas produced by the initial occlusion. Furthermore, it has been emphasized by Wiggers[7] that, while in acute experiments vasodilator drugs do not influence the functional state of myocardial regions deprived of blood by ligation, this does not preclude an increase in caliber of existing anastomoses nor the formation of new collaterals by such drugs in hearts with chronically narrowed or occluded arteries. It is in some such way that any influence of aminophylline or papaverine would be anticipated. For this reason, all the hearts used in this study had a post-mortem injection of the coronary system with a multicolored, radiopaque mixture to determine the influence these two vasodilator drugs might have had on the development or enlargement of anastomotic channels. The period of eight weeks between coronary ligation and termination of the experiment was chosen as being sufficiently long to permit the demonstration of such collateral vascular development. This estimate was based on the time for completed scar tissue formation in human myocardial infarction and on the time necessary for collateral development in chronic coronary occlusion experiments. As a further control of the development of collaterals a series of normal hearts were injected in which the coronary ligation (of the left anterior descending artery at the same site as in the other experiments) was performed post mortem.

METHOD

In a series of seventy-three dogs the left anterior descending coronary artery was ligated under aseptic precautions during anesthesia (nembutal, 25 mg. per kilogram). Artificial respiration was instituted, and the chest was opened by a 6 to 10 cm. long incision in the third or fourth intercostal space about 1 cm. to the left of the sternal margin. The pericardium was incised; the artery was isolated from the vein and ligated by means of silk. A fine, curved, ocular needle was used for the purpose. The tie was usually made just below the origin of the primary branch. In a small number, the primary branch was ligated instead, and in four instances the tie was made above the site of the primary branch. These variations were necessitated by the considerable variation in branching found in the different animals. The pericardial sac was not closed. The thorax was closed in layers with cotton thread, the pneumothorax was relieved, and the animals were permitted to breathe spontaneously. The animals were then allowed to recover from the anesthesia.

The animals were divided at random into three groups: (a) control, (b) aminophylline-treated,* and (c) papaverine-treated* groups. An equal number of dogs in the control and drug-treated groups were operated upon on the same day in order to insure comparable conditions. All dogs were housed and fed under similar conditions. They were kept in cages except that animals in the drug-treated groups were taken out for their daily drug injections.

Aminophylline was given in doses of 15 mg. per kilogram, the first dose intravenously immediately after ligation and the others subcutaneously twice daily for seven days and thereafter once daily for the remaining forty-nine days of the total eight-week course of treatment. Papaverine was administered in like manner except that the dose was 5 mg. per kilogram. The drugs were given as a 12 per cent aminophylline and 3.2 per cent papaverine hydrochloride solution in water.

*Aminophylline was kindly furnished by G. D. Searle and Co., Inc., through the courtesy of Dr. R. S. Kemp, and the papaverine hydrochloride by Parke, Davis and Co., through the courtesy of Dr. O. Kamm.

At the end of eight weeks the animals were sacrificed with nembutal and sodium cyanide and were autopsied. All the hearts were injected, dissected, and x-rayed* after the manner described by Schlesinger.[8] The pressure used for injection was constant (150 to 200 mm. Hg) in the different preparations, and so were the injection and x-ray techniques (for the latter, 40 kilovolts, 30 milliamperes, 2½ seconds, a fine focal spot, anode-film distance of 30 inches, paper-film holder, and nonscreen film were used). The prints of the x-rays used for the illustrations were made under comparable conditions. The infarct was examined before and after the heart was dissected. Contact tracings of the endocardial aspects of the infarcted areas were made on a glass plate and subsequently retraced on transparent paper. The areas of these retracings were measured with a planimeter. Check readings by the same and several other observers were found to agree within 9 per cent; this accords with the finding of Gold and his co-workers.[4] Sections for microscopic study were taken through the infarct, the transition zone, and in normal myocardium in all instances to compare the degree of healing in the three different groups.†

A group of twenty-nine normal dog hearts with post-mortem ties located at the site used in the operated dogs were injected. In fifteen, Schlesinger's lead-agar mixtures were used and in fourteen the mixture of lead carbonate-mercuric sulphide-gelatin used by Dock[9] and by Prinzmetal et al.[10] was employed. We have confirmed Schlesinger's observation that the lead-agar mixture penetrates arterioles less than 40 micra (and above 10 micra) in diameter in 30 per cent of our series. We have found that the lead-mercury-gelatin mixture which contains smaller particles penetrates vessels between 40 and 10 micra in diameter in 70 per cent of our cases. These facts were determined by measuring the size of the smallest injected vessels in microscopic sections with an ocular micrometer.

RESULTS

Of the seventy-three operated dogs, only forty-six were used in the final study. Twenty-one animals (27 per cent) were discarded because they did not survive the full eight-week postoperative period. Of these, thirteen succumbed within the first twenty-four hours after operation, an immediate operative mortality of 18 per cent. The cause of death in these latter animals was usually ventricular fibrillation or cardiac standstill during the operation. Data on these twenty-one dogs are summarized in Table I. Six other animals were rejected from the final study because of incomplete tie of the coronary artery, discovered at necropsy by vessel injection and dissection; there were no myocardial infarcts in this group.

TABLE I. DATA ON TWENTY-ONE DOGS THAT FAILED TO SURVIVE THE SET EIGHT-WEEK PERIOD AFTER LIGATION OF LEFT ANTERIOR DESCENDING CORONARY ARTERY

NUMBER OF DOGS	SURVIVAL PERIOD	CAUSE OF DEATH	REMARKS
11	Few minutes to few hours. Succumbed during operation or immediately after	Ventricular fibrillation or cardiac standstill	Three dogs were in puerperium and succumbed before coronary ligation
2	24 hours	Pulmonary edema or pneumonia	Irregularly outlined areas of myocardial hemorrhage and necrosis found
2	4 to 7 days	Empyema and sucking wound of chest	Indefinite areas of myocardial infarction about 2 to 4 cm.² found
4	10 to 18 days	Undetermined	Post-mortem examinations not done due to rapid decomposition during summer heat
1	10 days	Pneumonia. Cardiac failure? Cerebral hemorrhage?	Large, soft, necrotic infarct found
1	15 days	Distemper?	No evidence of myocardial infarction

*The x-rays were taken by the X-ray Department through the courtesy of Dr. R. Arens.

†The slides were prepared in the Department of Pathology through the courtesy of Dr. O. Saphir.

TABLE II. DATA ON ALL ANIMALS TREATED WITH AMINOPHYLLINE OR PAPAVERINE AND THE CONTROLS, WHICH SURVIVED THE EIGHT-WEEK EXPERIMENTAL PERIOD FOLLOWING LIGATION OF LEFT ANTERIOR DESCENDING CORONARY ARTERY AND WHOSE HEARTS WERE INJECTED ACCORDING TO SCHLESINGER'S TECHNIQUE

CONTROL					AMINOPHYLLINE-TREATED					PAPAVERINE-TREATED				
DOG	HEART WT. (GM.)	INFARCT AREA (CM.²)	$10^4 \times \frac{\text{AREA OF INFARCT}}{\text{HEART WT.}}$	TYPE OF ANAST.*	DOG	HEART WT. (GM.)	INFARCT AREA (CM.²)	$10^4 \times \frac{\text{AREA OF INFARCT}}{\text{HEART WT.}}$	TYPE OF ANAST.*	DOG	HEART WT. (GM.)	INFARCT AREA (CM.²)	$10^4 \times \frac{\text{AREA OF INFARCT}}{\text{HEART WT.}}$	TYPE OF ANAST.*
1	113	8.7	770	L-L	1A	123	6.2	504	con.	1P	152	5.1	336	L-L
2	112	11.8	1,054	con.	2A	114	8.2	719	unsuc.†	2P	153	9.8	641	L-L
3	222	11.4	514	unsuc.†	3A	120	9.5	792	L-L	3P	200	10.6	530	con.
4	102	11.5	1,127	L-L	4A	138	7.2	522	con.	4P	96	5.5	573	L-L
5	178	13.7	770	L-L	5A	106	6.3	594	L-L	5P	121	7.6	628	L-L
6	122	14.3	1,172	con.	6A	102	7.8	765	none	6P	100	5.7	570	L-L
7	90	11.5	1,267	L-L	7A	123	9.0	732	L-L	7P	117	5.0	427	none
8	123	7.4	602	none	8A	116	11.1	957	L-L	8P	110	5.3	482	L-L
9	93	6.1	656	none	9A	123	6.0	488	L-L	9P	120	6.4	533	L-L
10	163	9.7	595	none	10A	197	11.2	569	L-L	10P	100	6.2	620	L-L
11	198	9.2	465	L-L	11A	136	11.1	816	con.	11P	115	5.5	478	L-L
12	136	11.4	838	L-L	12A	113	7.5	664	L-L	12P	92	5.1	554	unsuc.†
13	80	13.9	1,738	L-L	13A	114	7.8	684	L-L	13P	78	6.6	846	L-L
14	132	9.0	682	L-L	14A	90	6.0	667	L-L	14P	83	4.9	590	L-L
15	144	12.0	833	L-L										
16	121	10.2	843	L-L										
17	128	11.0	859	L-L										
18	106	7.9	745	L-L										
Arithmetic mean			863		Arithmetic mean			677		Arithmetic mean			558	
Standard deviation			312.4		Standard deviation			133.6		Standard deviation			117.7	
					Arithmetic mean of controls minus arithmetic mean of aminophylline-treated animals = 863 - 677 = 186					Arithmetic mean of controls minus arithmetic mean of papaverine-treated animals = 863 - 558 = 305				
					Standard error of difference = 81.83					Standard error of difference = 80.16				

*Anast. = anastomoses. Using Schlesinger's nomenclature: Left to left (L-L) indicates anastomoses between branches of the left coronary artery; convergent (con.) indicates branches of one or both coronary arteries supplied by a mixture of blood from both coronary arteries.

†Unsuccessful injection.

1. *Infarct Size.*—Since the location of the tie was usually just below the primary branch of the left descending coronary artery, it is to be expected that in a larger heart a larger area is supplied by the occluded vessel and that therefore the infarct size varies, among other things, with the weight of the heart. This is actually shown to be true, when infarct size is plotted against heart weight although considerable scatter is seen (Fig. 1). The slope of the linear regression was 1 cm.^{2} increase in infarct size per 4.42 gram increase in heart weight. Since the heart weight averages in the three groups of animals are not the same, the papaverine-treated animals having a somewhat smaller average heart weight, it was considered advisable to calculate the infarct size per gram of heart weight in comparing the three groups. The pertinent data on the forty-six dogs constituting the final series are summarized in Table II. The mean size of the infarcted area per gram of heart weight was found largest in the untreated animals, intermediate in the aminophylline-treated group, and smallest in the papaverine-treated group, the arithmetic means being 0.0863,

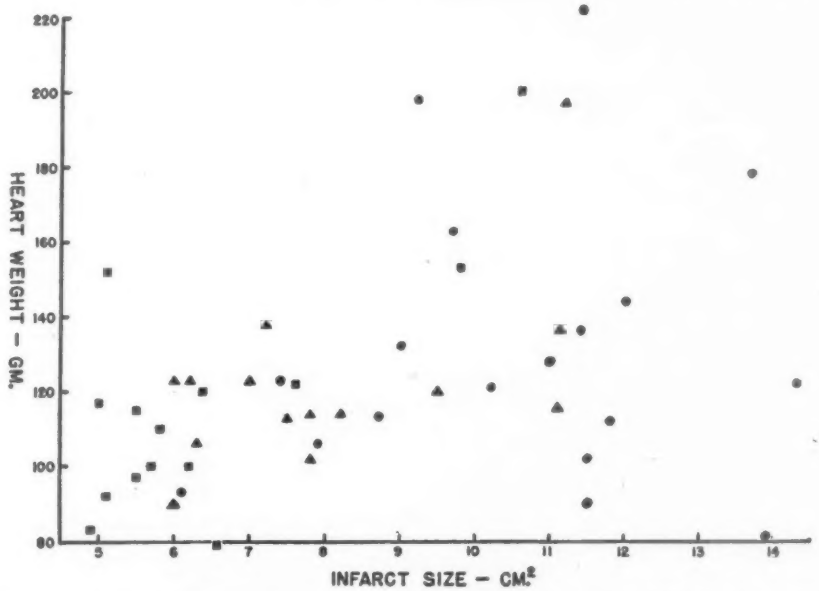


Fig. 1.—Scatter graph showing the degree correlation of infarct size to heart weight. • represents controls, □, papaverine-treated animals, and △, aminophylline-treated animals. Discussed in text.

0.0677, and 0.0558 cm.^{2} per gram, respectively. The difference of the means between the papaverine-treated and the untreated animals is 0.0305 cm.^{2} per gram, and the difference between the aminophylline-treated and the untreated animals is 0.0186 cm.^{2} per gram. These differences were found to be statistically significant; that between the papaverine and control animals was 3.8 times its standard error, and that between aminophylline and control animals was 2.3 times its standard error. The conventional value of two times the standard error is adopted for "significance." This puts the effect of the papaverine reducing action in a high range of probability, and shows a somewhat less effective action of aminophylline with a fair degree of probability. To illustrate the drug effects graphically, the frequency distribution of the various infarct sizes per gram of heart weight in the three groups is shown in Fig. 2. In the papaverine-treated animals the maximal frequency is clearly at a smaller infarct size per gram than in the control group. In spite of some overlap, the peak frequency is also clearly different in the aminophylline-treated animals.

Obviously even greater differences were obtained when the infarct size in the three groups were compared without correcting for differences in heart size. In the papaverine-treated group the mean infarct size was 6.41 sq. cm., in the aminophylline-treated group it was 8.06 sq. cm., and in the control group it was 10.6 square centimeters.

The position of the tie did not play any significant role since the infarct size could not be related to the location of the tie with respect to the primary branching. Furthermore, the different tie locations were scattered at random among the three groups.

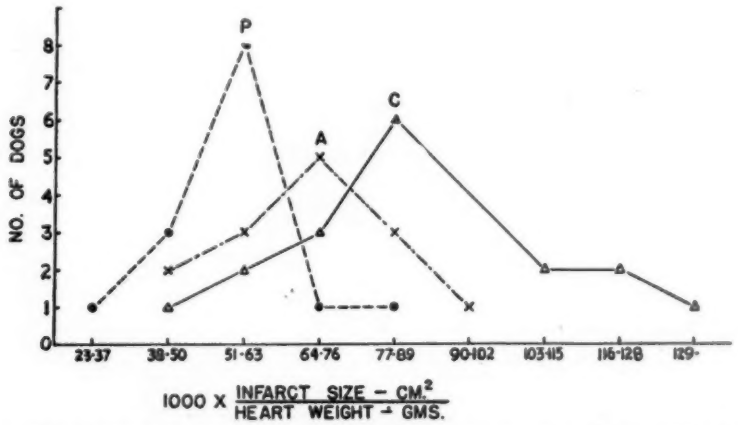


Fig. 2.—The frequency distribution of infarct size per gram of heart weight in the control (△-△), the aminophylline-treated (X-·-X), and the papaverine-treated (•---•) groups. These are labelled, respectively, *C*, *A*, and *P*. Discussed in text.

2. *Location and Gross and Microscopic Appearance of Infarcts.*—The infarcts were fairly uniform in form and location. The majority were roughly pyramidal in shape with the base of the pyramid located toward the cardiac apex. The infarct involved chiefly the apex and anterior wall of the left ventricle between the anterior papillary muscle and the septum. In larger lesions the anterior papillary muscle and septum were also involved. Occasionally the infarct involved the septum primarily (Fig. 3). In several instances, a narrow portion of the right ventricle adjacent to the septum was also infarcted. The subendocardial layers were involved more extensively than the subepicardial layers. However, there was almost always a thin strip of noninfarcted muscle just beneath the endocardium. In only four hearts were there "through and through" infarcts with pseudoaneurysm formation. The usual location of the infarct is shown in Fig. 4, a photograph obtained in a papaverine-treated animal which survived only ten days and showed at necropsy a soft yellowish-red infarct extending from endo- to epicardium. In general, the involved areas in the animals surviving eight weeks were sharply demarcated (Fig. 3), the ventricular wall was thin, measuring in some parts only 2 to 3 mm., and the muscle was replaced by gray fibrous tissue.

Microscopic analysis of the infarcts in the control, aminophylline and papaverine-treated groups failed to disclose any noticeable difference in the stage of healing in the three groups. A total of ninety-two sections were examined by independent observers without previous knowledge of the identity of the sections; the sections were taken from different regions of the infarcted and normal myocardium. Only four of the forty-six infarcts or 8.7 per cent showed the subacute stage of healing with pigmented macrophages, fibroblasts, and fine collagen formation; these were scattered between the treated and untreated

Fig. 3.—View of a dog's heart (12P, Table II) to show the appearance of the infarct eight weeks after ligating the left anterior descending coronary artery. The infarct is in an unusual location, being confined almost exclusively to the septum.

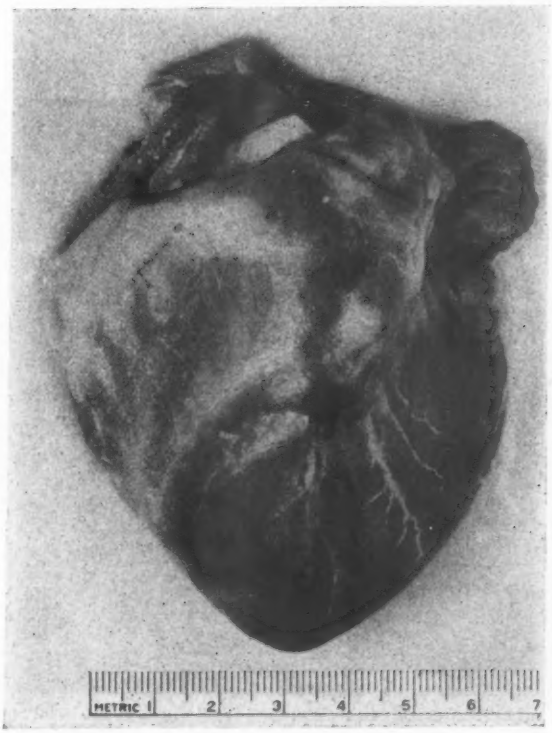
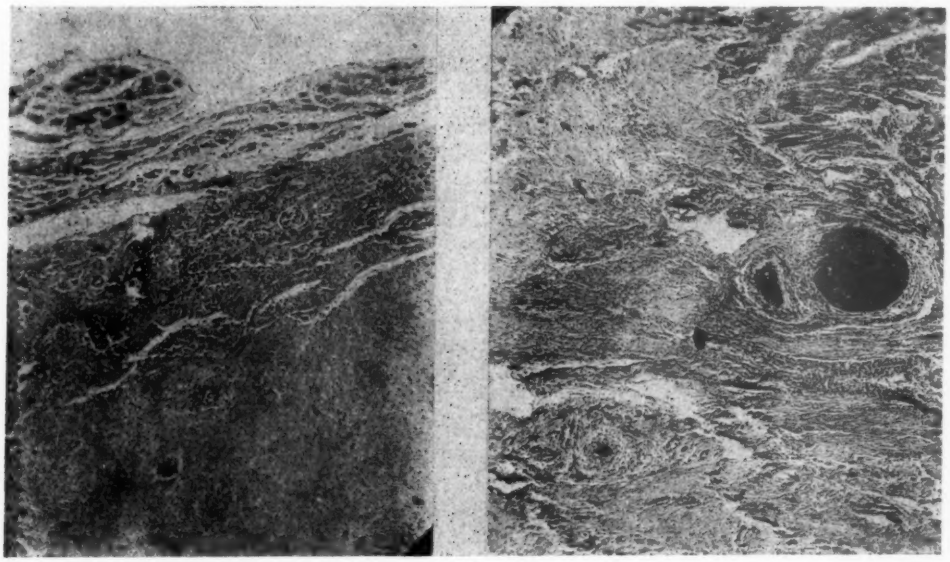


Fig. 4.—Anterior view of dog's heart showing topography of infarcted area resulting from ligation of the left anterior descending coronary artery. Dog survived ten days after ligating left anterior descending coronary artery. The infarcted area is the darker shaded region from the tie to the apex.

groups. All remaining sections showed the advanced stage of healing with compact arrangement of fibroblasts and dense collagen tissue (Fig. 5).

3. *Coronary Anastomoses.*—The anatomy of the coronary arteries of the dog has been adequately described in the literature (Spalteholz,[11] Moore,[12] and Pianetto[13]) and in general our observations of sixty-two injected hearts cor-



A. *B.*

Fig. 5.—Photomicrographs of myocardial infarcts. *A* shows a field in which a healing (above) and healed (below) infarct is present. Note uninvolved narrow subendocardial muscle, pigment, and dense collagen tissue from above downward. Section taken from Dog 9C, Table II (×75, hematoxylin-eosin). *B* shows a field in which a healed infarct and injected blood vessels are present. Note injected thickened arteriole in the lower left-hand corner. Section taken from Dog 5P, Table II (×50, hematoxylin-eosin).

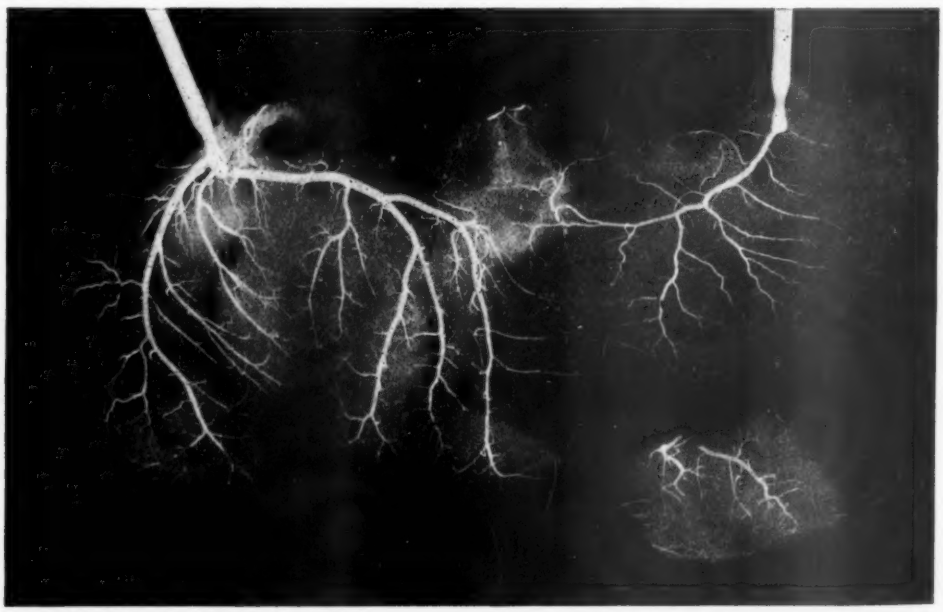


Fig. 6.—Coronary arteries of a normal dog showing predominance of the left coronary artery which is uniformly present in dogs. There are fine anastomoses between the left and right coronary arteries (in the circled area). This is an infrequent finding. Injected with lead-agar mixture.

TABLE III. INCIDENCE AND TYPE OF ANASTOMOSES IN HEARTS WITH INFARCTS EIGHT WEEKS AFTER TIE OF LEFT ANTERIOR DESCENDING CORONARY ARTERY

	CONTROL	AMINOPHYLLINE-TREATED	PAPAVERINE-TREATED	TOTAL
Successful injections	17	13	13	43
Unsuccessful injections	1	1	1	3
Left to left anastomoses*	11	10	11	32
Right to left anastomoses*	0	0	0	0
Convergent anastomoses*	3	2	1	6
No anastomoses	3	1	1	5

*See footnote of Table II. Right to left anastomoses indicates that branches of the left coronary artery are entirely supplied from the right coronary artery.

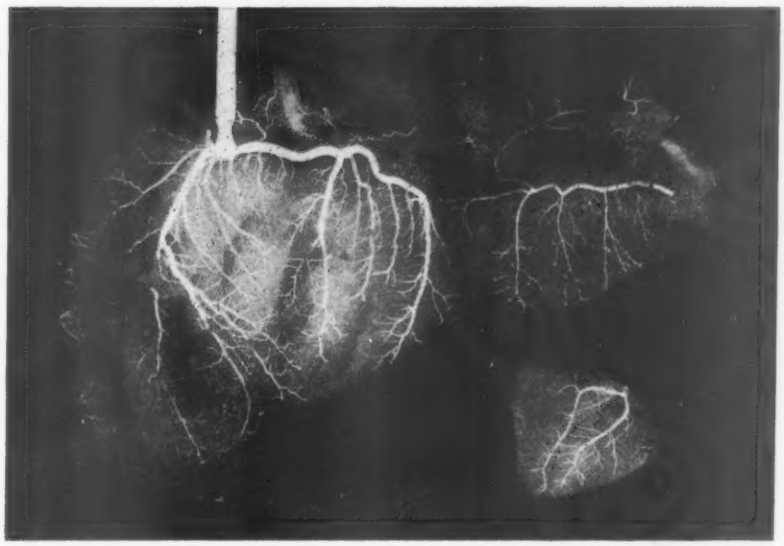


Fig. 7.—Coronary artery injection of Dog 14P (Table II) from papaverine-treated group, to show L-L anastomoses with retrograde filling distal to site of coronary occlusion made eight weeks prior (shown by arrow). Injected with lead-agar mixture. Infarct = 4.9 cm.^{2}

respond with these descriptions. It should be emphasized that the left coronary artery is uniformly predominant in the dog (Fig. 6), whereas this left dominance occurs in only 20 per cent of human hearts.[16]

In Tables II and III are summarized the presence and type of anastomoses encountered in the dogs with coronary ties and myocardial infarcts which survived eight weeks; the terminology followed is that suggested by Schlesinger.[8] It will be seen that anastomoses developed in the vast majority of cases, but in a few (11.6 per cent) they failed to appear. No instance of right to left anastomoses was encountered, a small number were convergent anastomoses, but in most of the cases the anastomoses were left to left. This is also true in man even in instances in which the right coronary artery is predominant.[8]

There was no correlation between the presence or extent of the anastomoses and the size of the myocardial infarct. Furthermore, no difference was observed between the treated and untreated groups of cases. Nor could any difference be observed in the vascularity demonstrated on injecting lead-agar mixture between the treated and untreated cases. Examples of left to left or convergent anastomoses in three instances of myocardial infarction are shown in Figs. 7, 8, and 9.

While the frequency of anastomoses was not significantly different in the three groups with infarcts, there was clear evidence that in all three groups the presence of the coronary tie for eight weeks had definitely increased the frequency of anastomoses when compared with normal hearts. Thus when the

Fig. 8.—Coronary artery injection of Dog 11A (Table II) from aminophylline-treated group to show convergent anastomoses with retrograde filling distal to site of coronary occlusion made eight weeks prior (shown by arrow). Injected with lead-agar mixture. Infarct = 11.1 cm.²

Fig. 9.—Coronary artery injection of Dog 7C (Table II) from control group to show L-L anastomoses with retrograde filling distal to site of coronary occlusion made eight weeks prior (shown by arrow). Injected with lead-agar mixture. Infarct = 11.5 cm.²

entire series of animals surviving eight weeks after coronary tie were compared with a series of animals with ligation post mortem in which the same injection material was used, namely lead-agar mixture, the frequency of anastomoses was strikingly different, viz., 88.4 per cent in the former compared with 13.3 per cent in the latter (Table IV). Two instances of absent anastomoses when injected with lead-agar mixture in these post-mortem ties are shown in Figs. 10 and 11.

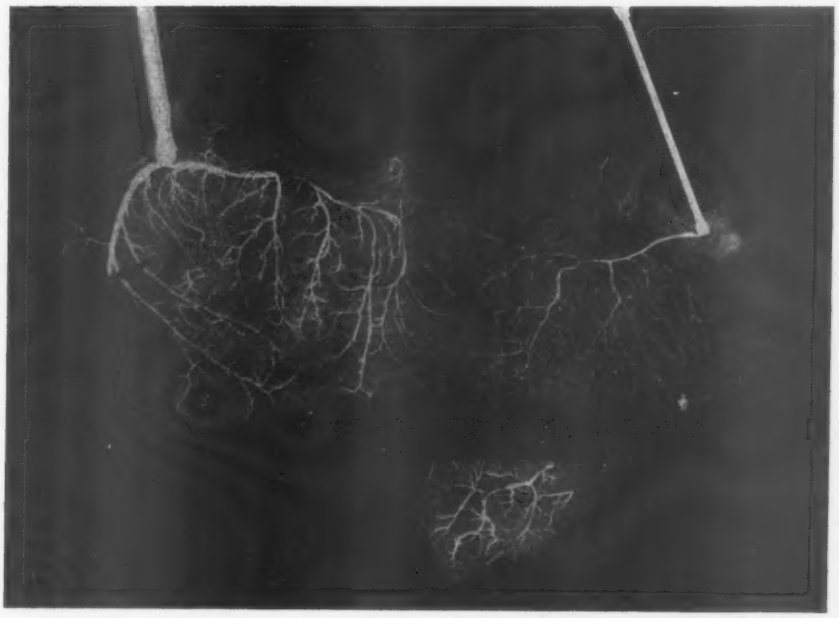


Fig. 10.—Coronary artery injection of dog to show absence of any anastomoses distal to site of post-mortem tie of coronary artery (shown by arrow). Injected with lead-agar mixture.

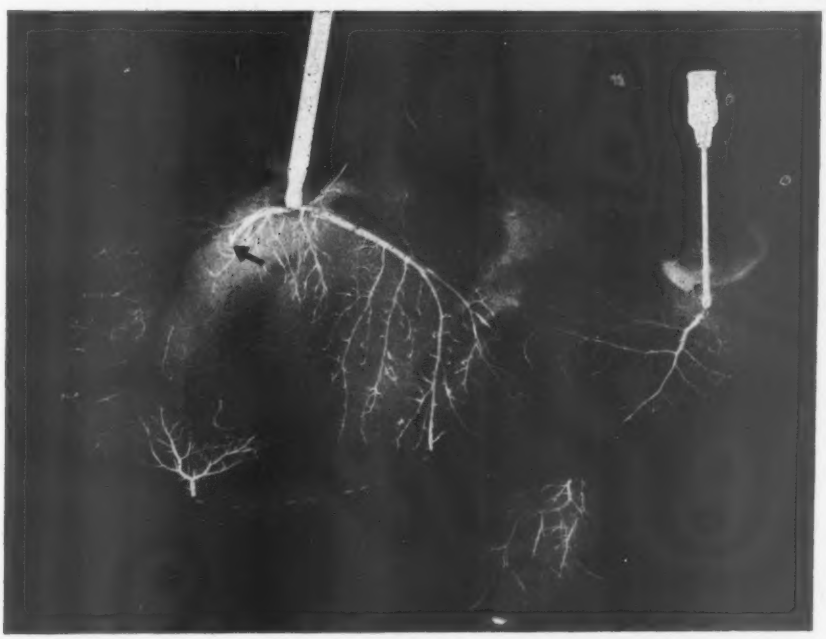


Fig. 11.—Coronary artery injection of dog to show absence of any anastomoses distal to site of post-mortem tie of coronary artery (shown by arrow). Injected with lead-agar mixture.

TABLE IV. COMPARISON OF ANASTOMOSES IN HEARTS WITH INFARCTS EIGHT WEEKS AFTER CORONARY TIE AND NORMAL HEARTS WITH POST-MORTEM CORONARY TIE OF LEFT ANTERIOR DESCENDING CORONARY ARTERY

	HEARTS SURVIVING EIGHT WEEKS AFTER TIE	NORMAL HEARTS WITH POST-MORTEM TIES	
	LEAD-AGAR MIXTURE*	LEAD-AGAR MIXTURE*	LEAD-MERCURY-GELATIN MIXTURE†
Anastomoses	38	2	10
No anastomoses	5	13	4
Totals	43	15	14

*Lead-agar was injected mainly into vessels over 40 micra (see text).

†Lead-mercury-gelatin was injected into vessels between 10 and 40 micra in 70 per cent of cases.

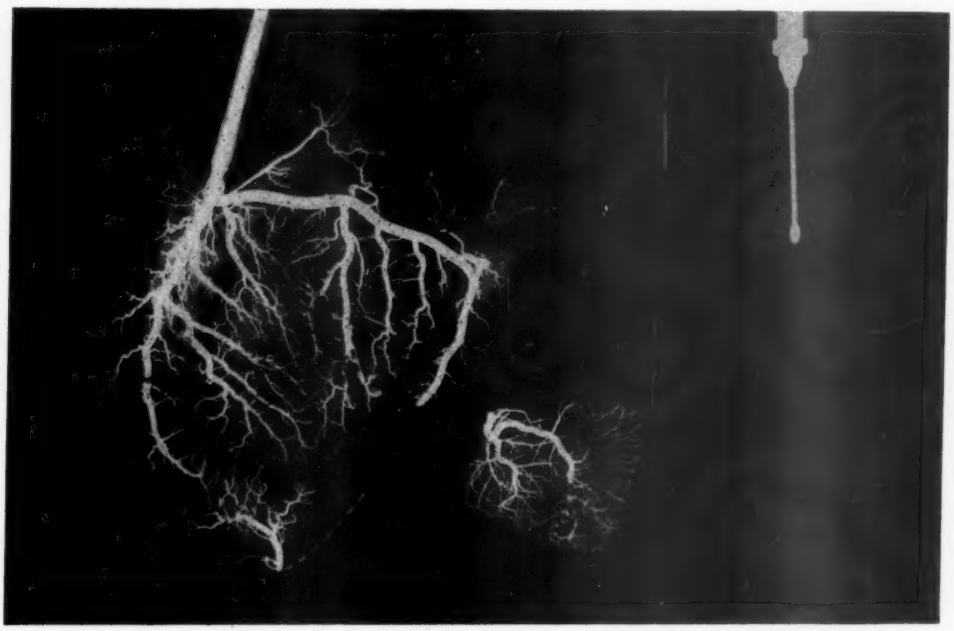


Fig. 12.—Injection of left coronary artery only showing the absence of L-R anastomoses but the presence of L-L anastomoses, with retrograde filling distal to site of post-mortem tie (shown by arrow). Injected with lead-mercury-gelatin mixture.

These findings do not deny that anastomoses will be readily demonstrated in the normal dog's heart if a fine enough injection material is used. The extent of visualization depends on the size of the communicating channels and the size of the particles of the mass used to inject them. When one coronary artery is perfused with saline we have found that the fluid flows out of the other artery. Innumerable anastomotic channels are easily seen on the surface of the heart when India ink is injected into the coronary arteries. However, using the lead-mercury-gelatin mixture, which has smaller particles than the usual radiopaque materials used, and injecting only the left coronary artery under normal pressures (150 to 200 mm. Hg), one does not ordinarily see anastomoses between the left and right coronary arteries (Fig. 12). This is at variance with the observations of Prinzmetal et al.,[10] who were able to inject the entire coronary system in normal human hearts by injecting one branch of the left coronary artery. In the dog, communications between the ventricular branches of the right coronary artery and the right ventricular branches of the left coronary artery can be demonstrated only infrequently. Such an instance is illustrated in Fig. 6. With the lead-mercury-gelatin mixture, however, fine anastomoses

are abundantly demonstrated between the anterior descending, marginal, and circumflex branches of the left coronary artery (Fig. 12).

That the size of the injecting material determines the number of anastomoses demonstrated was shown by comparing a series of fourteen hearts with post-mortem coronary ties injected with lead-mercury-gelatin with a group of fifteen hearts with post-mortem coronary ties injected with lead-agar. As Table IV shows, the percentage of cases with anastomoses in the former is 71.4 per cent compared with 13.3 per cent for the latter. The difference can also be appreciated by comparing Figs. 10 and 11 with Fig. 13.

It was observed over and over again that, when anastomoses are present, the vessel having a tie on it, whether placed there eight weeks before or at post mortem, fills from below indicating the absence of leakage past the ligature.

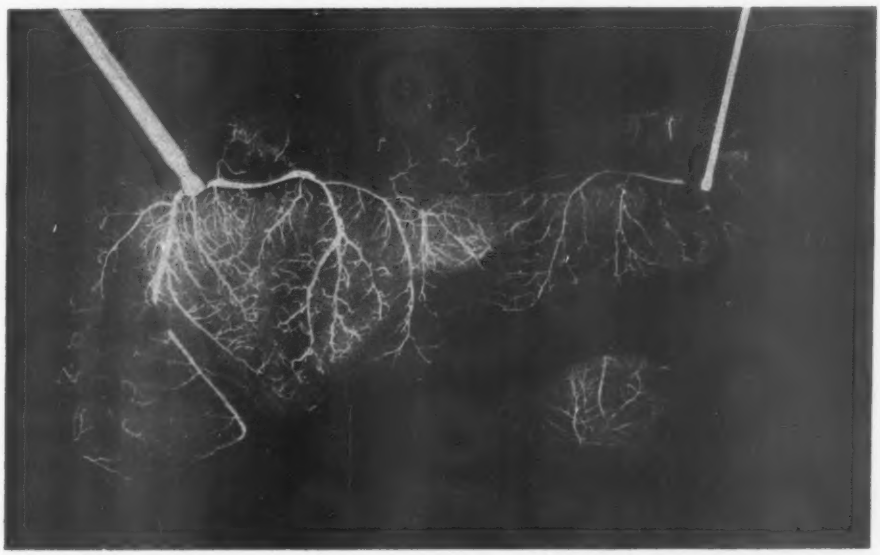


Fig. 13.—Coronary artery injection showing L-L anastomoses with retrograde filling distal to site of post-mortem tie (shown by arrow). Injected with lead-mercury-gelatin mixture.

It is significant that the lapse of time after ligating a coronary artery makes the demonstration of anastomoses easy even with injection media with larger particles. Our data on animals surviving the coronary tie for less than eight weeks are too incomplete to warrant any statements on the time it takes for collaterals to develop and enlarge. However, we have inadvertently made observations on the effect of pericardial adhesions on these collateral channels. In two instances, a gauze sponge, 4 by 3 cm., was left in the pericardial sac. At necropsy, many adhesions between the scarred myocardium and parietal pericardium could be demonstrated. The hearts with these adhesions failed to reveal any additional vascular channels to the myocardium by way of the adhesions. This is in accord with the findings of the more systematic study of vascularization by pericardial adhesions made by Burchell.[14]

DISCUSSION

The fact that myocardial infarcts develop when a single major artery like the left anterior descending artery is occluded shows that the coronary arteries are end arteries even though anastomotic communications can be demonstrated in many instances. While these communications can supply some blood to the region rendered ischemic by coronary occlusion, they are inadequate to make

up entirely for the deficit in blood supply. In this sense, then, the coronary arteries in the dog, and, presumably in man, are end arteries physiologically. Coronary arteriosclerosis tends to alter this condition by stimulating the development of a more adequate collateral anastomotic system so that occlusion of single large coronary artery branches need not lead to myocardial infarction. Myocardial infarcts in the presence of coronary sclerosis usually develop only when more than one of the coronary arteries supplying a region are narrowed or occluded, as earlier work has demonstrated.[15]

Our results have shown that coronary vasodilator drugs have an effect on infarct size. Infarcts in papaverine-treated dogs are definitely smaller than those in untreated animals. Aminophylline also has a statistically significant effect, but less striking than that of papaverine. Our experience, therefore, supports the use of such vasodilators in treating recent myocardial infarction. Of course these drugs should be given in adequate amounts and frequently enough so as to have a sustained effect of sufficient intensity. The route of administration chosen should also be one which ensures that the drug gets to the coronary vessels in adequate quantities. Papaverine can be given either orally or parenterally, but in the case of aminophylline the question may be raised whether oral administration is effective. Reduction in the size of the ischemic area is of value in lessening the amount of heart muscle which remains impaired and nonfunctioning and so should lessen the occurrence and extent of heart failure and also the acute coronary insufficiency of the regions of the heart not primarily involved by the occlusion. If generalized, coronary "spasm" accompanies infarction, the vasodilator drugs will also tend to neutralize this effect. Papaverine has other advantages in that it is a mild sedative and is valuable in preventing active ectopic rhythms.[2, 3]

Although a better blood supply to the heart areas supplied by the occluded coronary artery must be postulated to account for the smaller infarct size in the drug-treated dogs, this could not be demonstrated by injection of the coronary system eight weeks after coronary ligation. Size and extent of the vascular bed to the ischemic area demonstrated by the method employed were of the same order in the papaverine-treated and in the aminophylline-treated dogs as in the untreated ones. There are two possible explanations for this apparent paradox.

First, the size and extent of the vascular bed which was formed to supply the ischemic area at the end of eight weeks gave no clue as to the rate at which this vascularization developed. Examination at the end of eight weeks shows the extent of the maximum blood supply then existing regardless of whether this development took place slowly or rapidly. However, since the enlargement of collaterals appears to depend, among other factors, upon the pressure gradient across the anastomotic communications, those that develop rapidly at first would cause a lowering of the pressure gradient and therefore develop more slowly later in comparison with those that develop sluggishly at first. After a time, therefore, the more slowly developing anastomoses would, as it were, catch up with those which started to develop brusquely. Vasodilator drugs would be expected to facilitate the early rapid development of collaterals by dilating the coronary vessels leading to the communicating vessels. This is due to the fact that such vasodilatation increases the pressure gradient across the anastomosis by lessening the pressure gradient from the aorta to the junctions of these anastomoses with the patent coronary arteries. The earlier development of collaterals in the drug-treated dogs would lessen the ischemia of the peripheral areas of the ischemic region sufficiently to prevent them from becoming necrotic.

The vasodilatation in the drug-treated animals not only facilitates the early growth of anastomotic channels but, in addition, provides a greater blood supply through dilatation of channels already existing. The size of the vascular bed revealed by necropsy injection does not necessarily give the picture existing during life, since it ignores vasomotor tone. Even with the same extent of anastomotic channels, the vasodilator drugs provide a larger bed with a greater blood flow than is present in an untreated animal.

From our results the following conclusions are drawn:

(1) The action of papaverine and, to a lesser extent, aminophylline on infarct size is to provide a greater blood flow to the ischemic area by decreasing the vasomotor tone of the coronary vessels and by facilitating the early development of collateral channels when the ill effects of ischemia can be compensated for most adequately and necrosis avoided.

(2) Collateral circulation is present even before the coronary artery ligation since a large percentage of control animals show injectable channels after post-mortem coronary tie when a medium of small-sized particles like the lead-mercury-gelatin mixture is used for injection. Such channels are found to be increased in size eight weeks after the coronary tie since they are then more readily filled even with larger-sized particles such as found in the lead-agar mixture. The enlargement and development of the coronary collaterals are brought about by the altered pressure gradient following coronary occlusion. Normally there is little pressure drop across these interarterial communications, but following coronary occlusion a marked pressure drop occurs which, operating over a period of time, leads to their enlargement on a purely mechanical basis. This enlargement is, of course, favored by the loss of vasomotor tone consequent to the vasodilator action of local ischemia, and, in the case of the drug-treated animals, it is further facilitated by the vasodilator effect of the drugs.

SUMMARY

1. Papaverine and aminophylline, when given for a period of eight weeks in amounts comparable to therapeutic and nontoxic doses in man, reduce the size of experimental myocardial infarcts in dogs. Papaverine is more effective than aminophylline in this respect.

2. There is an anatomic increase in the size and number of anastomotic channels in infarcted hearts with occlusion of a main coronary artery as compared with normal hearts. This was demonstrated by injection technique.

3. No difference in the stage of healing was seen microscopically between the treated and untreated dogs at the end of eight weeks.

4. The difference in infarct size between the treated and untreated dogs was not associated with any anatomic difference in the post-mortem demonstration of the extent of the anastomoses. It is concluded that the difference in infarct size was, therefore, due to a larger caliber of these anastomotic channels during life in the drug-treated dogs because of coronary vasodilatation and, probably, also to their more rapid early development. In these two ways the marginal area of the ischemic region was rendered sufficiently less ischemic as not to become necrotic.

5. It is concluded that the rationale of early vasodilator therapy in recent myocardial infarction has been demonstrated and that both aminophylline and papaverine, especially the latter, have been shown to be effective.

We are indebted to various members of the department for assistance in the conduct of these experiments, and to Mrs. J. Meyer for her help in the statistical analysis of the data.

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PRIMARY TUMOR OF THE LEFT AURICLE SIMULATING MITRAL STENOSIS

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TUMORS of the heart, though rare, are of considerable interest. Statistics compiled by Mead show that primary tumor of the heart occurred in 0.03 per cent of all autopsies (40,000).[1] The literature on this subject up to 1931 has been thoroughly reviewed by Yater,[2] and since then by Mead,[1] Gilchrist and Millar,[3] and more recently by Lisa, Hirschhorn, and Hart.[4]

The possibility of the existence of such a pathologic state must be considered more frequently in differential diagnosis of heart disease of undetermined etiology. It is only by careful observation, frequent clinical examinations, and accurate followup of cases, with this condition in mind, that more exacting criteria for early diagnosis may be added to the literature. Only two cases have been reported in which the diagnosis was made before death and confirmed by autopsy. In both cases the tumors were malignant.[5, 6]

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Recent reports in the literature[7] describe the removal of an intrapericardial teratoma as well as a tumorlike mass located in the left ventricle. An advance of this nature in intrathoracic surgery serves to stimulate the reporting of all cases of cardiac neoplasm with the hope that eventually a satisfactory symptom complex for early diagnosis may be achieved.

The purpose of this paper is to present a case of primary tumor of the heart diagnosed as mitral stenosis in a 48-year-old woman. The presenting signs, electrocardiographic and x-ray studies, were confirmatory of this diagnosis. The atypical course during the last few days of life was explained on the basis of unusual complications. It is this atypical course that recently has been re-emphasized as being most helpful in the diagnosis of heart tumor.[8] Certain pathologic observations made in this case suggest that hemorrhage into the tumor may have originated earlier than might have occurred if the use of digitalis had been omitted.[9]

The following report is of interest in several respects and adds another case of primary tumor of the left auricle to the already accumulated literature.

CASE REPORT

A 48-year-old married woman presented herself to her family physician with complaints of exertional dyspnea, chest pain, cough, weakness, and menopausal symptoms. Physical examination was negative except for a soft mid-diastolic murmur at the mitral area, heard only in the left lateral decubitus and accentuated by moderate exercise. She had been under the care of a competent internist for some time previously. The diagnosis of heart disease was a complete surprise to the patient, as she had been reassured many times concerning her cardiac status. An electrocardiogram taken at this time (Fig. 1) showed regular sinus rhythm at a rate of 100. There was slight right axis deviation. There was a prominent P_2 and P_3. Lead IVF showed a small R_4. There was a tendency to low voltage and some slurring of the QRS complexes.

The x-ray findings (Fig. 2) by Dr. K. L. Mitton were reported as follows:

Examination of the chest showed that the left side of the bony cage was slightly fuller than the right. The aorta was well within the limits of normal in size. There was considerable fullness of the left auricle and in the outflow of the right ventricle. The diaphragms were smooth and the angles were clear. There was an increase in density of the hila which was consistent with pulmonary congestion, and there was generalized stippled increase in the density throughout the chest.

Impression.—Mitral stenosis with slight pulmonary congestion and pulmonary hemosiderosis was present.

The attending physician decided to place the patient on complete rest in bed, and digitalization was attempted. Since this medication was poorly tolerated, a brand of lanatosid-C was substituted. The patient's general condition remained satisfactory during the ensuing week. However, the next afternoon and evening, dyspnea became increasingly severe, even at rest, and the following morning the attending physician received an urgent summons to the home of his patient. She appeared in extremis and was breathless, with cold, damp extremities and marked pallor; the clinical picture suggested peripheral circulatory failure. The blood pressure was 80/60. The pulse was feeble and irregular; the rate was 148. She was admitted to the hospital.

On examination, after hospitalization, the patient was seen in a semiupright position, receiving oxygen by tent and showing extreme restlessness. She was pale, with cold extremities, and apprehensive. She complained bitterly of pain in the lower lumbar spine, referred up to the cervical region and out toward both shoulders. The neck veins were not distended, the heart sounds were mainly regular, with occasional extrasystoles, of good quality and with a rate of 120. A presystolic murmur was detected at the mitral area. The lungs were clear anteriorly, but there was dullness in the right base, and a few râles were heard in this area. The abdomen was tender and moderately distended, and the liver was enlarged 3 finger-breadths below the costal margin. There was no ascites or peripheral edema.

We were faced, therefore, with a seriously ill patient who had an emergency hospital admission. She was presented as a case of mitral stenosis, who had been on bed rest for

one week, more or less completely digitalized, and who, after some minor dyspnea the preceding evening, suddenly went into shock. The natural thought was to review the common complications of mitral stenosis, such as are given by White[10]: (1) Pulmonary congestion without heart failure (due to a tight mitral valve); (2) right ventricular failure; (3) auricular fibrillation; (4) embolism either into the arterial circulation or pulmonary in nature, as a paradoxical embolus or from a deep leg vein phlebitis; and (5) paroxysmal tachycardia.

In addition to these considerations the possibility of an abdominal disorder, such as mesenteric thrombosis, or an acute surgical abdomen superimposed on heart failure, was entertained. A ball-valve thrombus in the left auricle was considered as well. However, the abrupt clinical changes from a critical to a greatly improved state tended to rule out mesenteric thrombosis.

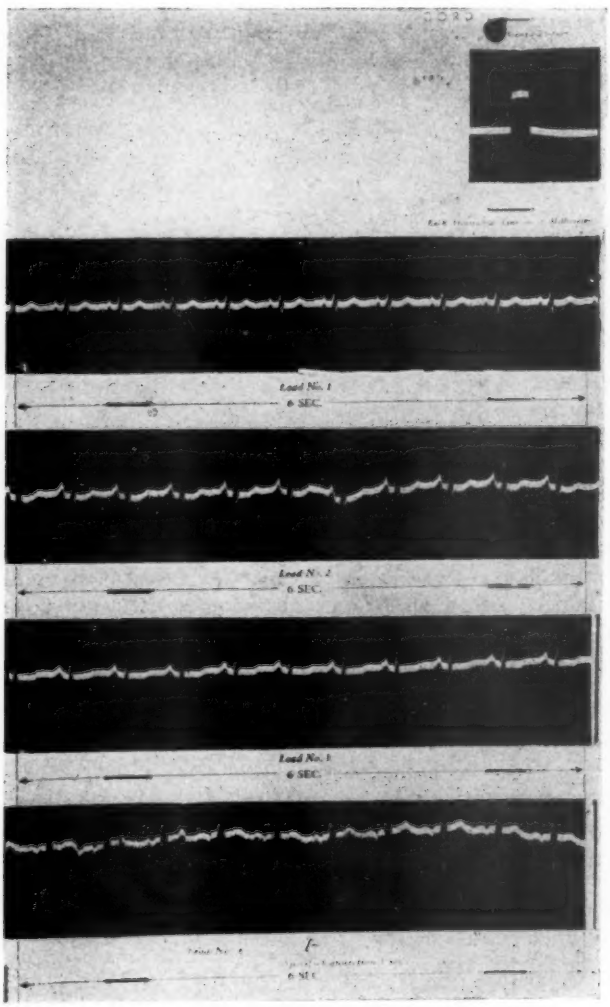

Fig. 1.—Electrocardiogram showing slight right axis deviation and prominent P_2 and P_3.

Although certain findings of the examination suggested the possibility of pulmonary infarction, others pointed toward right ventricular failure with hepatic engorgement.[11] A careful appraisal of the entire picture showed serious contradictions among the signs suggesting either of these conditions. It was difficult to correlate the extremely ill state of the patient with the findings detected on physical examination. On the basis of sudden engorgement of the liver, with absence of distension of the neck veins, the diagnosis of acute right ventricular failure seemed a possibility, especially with dullness and râles in the right base (due to upward enlargement of the liver).[11]

Since the primary pathologic condition was considered as mitral stenosis, the possibility of associated interauricular septal defect (Lutembacher's disease) with retrograde embolism from the left auricle, its appendage or the mitral valve causing a pulmonary infarction in the base of the right lung or traveling down to block the inferior vena cava and resulting in sudden liver enlargement, was considered.

It was evident that other complications of mitral stenosis, such as embolism somewhere in the arterial circulation, was not a clinical problem and that auricular fibrillation was not present, as the early arrhythmia was transient and due to ventricular extrasystoles. Paroxysmal tachycardia was easily ruled out by the gradual fall in pulse rate.

The patient received active and supportive treatment with oxygen, Coramine, caffeine sodium benzoate, Cedilanid, and small doses of morphine with atropine. During the next twelve hours she seemed improved, her pulse became strong, and the rate began to fall gradually. The following morning she was catheterized and 18 ounces were obtained. The next day she seemed improved and much less apprehensive, the pulse rate was 108, of good quality, and regular. The blood pressure was 107/74. She had rested well during the night and the skin was pink and warm; she had an occasional dry cough, but the lungs were clear. She had been unable to retain fluid, so a clysis of 500 c.c. of saline with 2.5 per cent glucose was given at 10:30 A.M. and 6:30 P.M. She took fluid easily the next day, retaining 1,370 c.c. in twelve hours with an output of only 270 cubic centimeters. Examination showed a distended bladder, and 12 ounces were obtained on catheterization. The back pain had disappeared, breathing was improved, and oxygen was discontinued. The right lung had cleared,

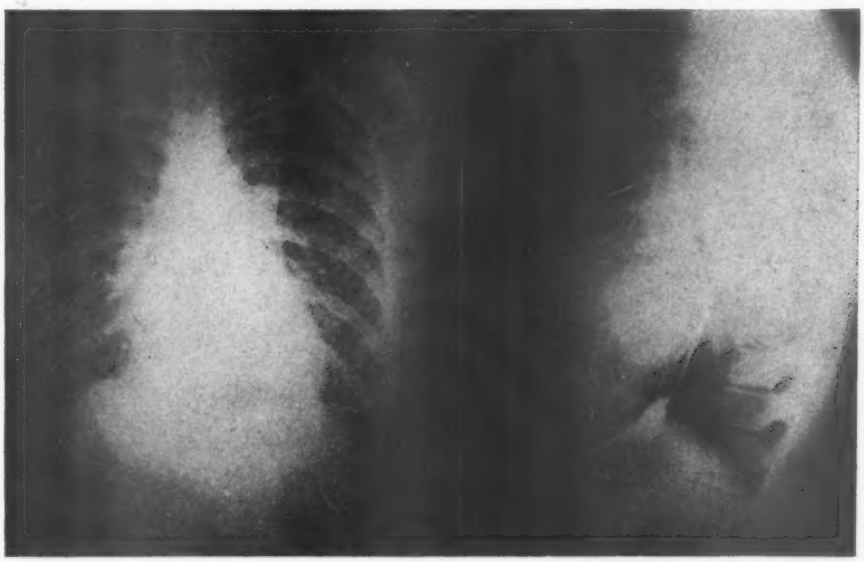

Fig. 2.—Roentgenogram of heart and lungs suggesting mitral stenosis.

the liver was barely palpable, the patient tolerated light nourishment, and during the ensuing twenty-four hours the fluid intake was 1,780 c.c. with 990 c.c. output. Although the general picture suggested gradual but steady improvement, it was apparent she was more comfortable in the upright position. The patient had several sudden attacks in which there was an abrupt transition from reasonable progress to a gravely ill state. When in this condition, the findings were similar to those noted on admission. The following twelve hours the intake was 980 c.c., and the output fell to 0. The admission temperature was 98° F. and rose to 102° F. on the third hospital day. It remained at the level of 100° F. until the death of the patient. The respiratory rate was 30 on admission, fell to 22 on the second day, and remained at this rate until the final episode. Very suddenly the patient had an attack similar to that described on her admission, the pulse became small and feeble, and blood pressure readings were unobtainable. One-fourth grain of morphine seemed to improve her condition rapidly, but a half hour later a similar attack occurred, and the patient died suddenly, six days after being admitted.

Laboratory Findings.—Hemoglobin, 81 per cent; erythrocytes, 4,100,000; leucocytes, 28,000; icteric index, 18; carbon dioxide combining power, 38 vol. per cent; urea nitrogen, 53 mg. per cent. Urine: albumin, 2 plus; sugar, absent; few hyaline casts in the sediment.

Necropsy.—An examination of the body was performed two hours post mortem. The body was that of a fairly well-nourished and well-developed white woman. The face and neck were deeply cyanotic. The pupils were 4 mm. wide, round, and equal. There was no definite jaundice and no edema. When the sternum and the adjacent ribs were removed, the left pleural cavity was found to contain about 500 c.c. of clear straw-colored fluid. No fluid was found in the right cavity. Each pleural cavity was free of adhesions. The heart, when freed from blood clot, weighed 400 grams. It was globular in shape, moderately enlarged, and in diastole. The epicardial surface showed nothing of note. On opening the left auricle a soft but resilient tumor mass was found filling the entire cavity. The tumor consisted of a roughly globular, polypoid growth, 6 by 5 by 6 cm., the external surface of which was slightly lobulated, glistening, grayish green, and devoid of any signs of recent thrombosis.

Fig. 3.

Fig. 4.

Fig. 3.—Photograph showing pedunculated myxoma attached to the interauricular septum of the left auricle.

Fig. 4.—Photomicrograph (×300) of the heart tumor showing delicate blood vessels, fusiform and stellate cells in a mucoid matrix.

It was attached by a broad base to the interauricular septum just above the upper border of the closed foramen ovale (Fig. 3). When first seen the tumor rested snugly in the mitral orifice, but it could be displaced above the valve base. A longitudinal bisection of the tumor showed the base mottled red and brown while the periphery varied from a translucent yellow green to gray and resembled gelatinous material. The ventricles were both moderately dilated, particularly the right one, and the walls of the latter chamber were considerably hypertrophied. The valve measurements were all within normal limits. The cusps and leaflets of all valves showed no evidence of vegetations, and there was no scarring to suggest previous valvular injury. All chambers were free of thrombi. The root of the aorta had a smooth intimal surface. The coronary arteries were thin walled and patent. Both lungs showed an increased firmness, and the cut surface was that of chronic passive congestion. The peritoneal cavity contained no free fluid. The liver weighed 1,350 grams. The capsule was smooth. The cut surface showed the parenchyma pale, golden brownish yellow, and the centers of the lobules were quite prominent. The gall bladder was normal. The remaining organs were examined and showed nothing of pathologic interest except for the effects of circulatory failure.

Anatomic Diagnoses.—The anatomic diagnoses were: tumor of the left auricle obstructing the auriculoventricular orifice; brown induration of lungs; and chronic passive congestion of liver, spleen, and kidneys.

Microscopic (Fig. 4).—Sections of the heart tumor revealed a rather acellular matrix stained with various degrees of intensity, partly eosinophilic and partly basophilic. The cells in the loose network of the intercellular substance were elongated and fusiform in shape. Stellate forms with delicate, anastomosing fibrillary processes were also seen. A small proportion of round and oval cells with distinct cell membranes and compact nuclei were found about capillaries and blood spaces where they occasionally formed radial palisades. Scattered throughout the tumor were multinucleated cells with scant and pale cytoplasm. Wavy elastic fibers were seen in the section stained by the Weigert elastic tissue method. The periphery of the tumor was covered with flattened endothelium-like cells. Extravasation of erythrocytes and numerous hemosiderin-containing phagocytes were found at the base of the tumor. Selected sections through the interauricular wall at the site of attachment of the tumor showed it to originate from subendothelial connective tissue without interruption of the medial elastic fiber network of the endocardium. The vessels in the subendocardial tissue were quite tortuous and had thickened walls. The myocardium revealed no evidence of rheumatic disease.

The lungs showed considerable passive congestion, hemosiderosis, and edema. Signs of passive congestion of longer duration were found in the liver, spleen, and kidneys.

Fig. 5.—Photomicrograph (×300) showing surface of tumor with endothelial covering and subjacent tissue beneath which is fresh hemorrhage. Note vascularity of the tumor.

DISCUSSION

A tumor found in the heart may be a true neoplasm or a thrombus. Tumors of the heart were observed by the old anatomists and classified as polypi cordis. In 1685, Zollicoferus[12] wrote a dissertation on the subject "De polypo cordis." Richard Link[13] reviewed the literature from 1824 to 1908 and tabulated ninety-one primary neoplasms of the heart. In 1923, Mandelstamm[14] collected 143 primary tumors of the heart, of which 117 were benign and twenty-six were malignant. Yater, in 1931, brought the total of heart neoplasms to 150 and, in 1941, Lisa, Hirschhorn, and Hart added thirty-three more cases from the literature.

All primary neoplasms of the heart are of mesoblastic origin; fibroma, myxoma, sarcoma, and rhabdomyoma predominating. They occur in any portion of the heart. Myxoma is the most common and the most debated type of cardiac tumor. Thorel[15] believed that myxomas are merely degeneration forms of organized thrombi. In a series of articles on tumors of the heart he analyzed twenty-four cases reported as myxomas and stated that they were all, except one, organized thrombi. Stahr,[16] Karrenstein,[17] and Husten[18] also believed that most endocardial myxomas were thrombi in various stages of organization. Ribbert,[19] on the other hand, is inclined to think that most of the tumors described as myxomas are true neoplasms originating from rests of embryonic mucoid tissue, which persists at times, especially in the rim of the foramen ovale. He emphasized that (1) the masses are usually too large to be organized thrombi, (2) it is difficult to conceive of thrombi forming in otherwise normal hearts not showing the slightest evidence of previous endocarditis or trauma, and (3) myxomas occur exclusively in the auricles whereas thrombi occur just as frequently, if not more so, in the ventricles. Ewing,[20] in his book *Neoplastic Diseases,* states that separation of myxomas from organized thrombi may be based on the highly mucinous character of the stroma, and on the presence of orderly radiating blood vessels and elastic fibers. He continues, "it seems unlikely that a simple organizing blood-clot can reproduce the positive features of the true myxoma. Hence the great majority of the reported cases of cardiac myxoma are probably genuine."

Considering our case, the size of the tumor, the site of attachment, the absence of layer formation (as would be expected in a thrombus), the healthy state of the endocardium, and the histologic structure all seem to indicate that the tumor described above represents a true neoplasm. The presence of hemorrhage at the base of the tumor is of recent origin and is easily explained by the delicate structure of the vessels and the mechanical conditions to which the tumor was subjected. Digitalis administration and forced contraction of the myocardium may have been contributory.

Various attempts have been made to classify cardiac neoplasms on a clinical basis, so as thereby to facilitate their diagnosis during life. (Link,[13] Meroz,[21] and Yater,[2] have each proposed classifications.) From a consideration of the case reports, it is apparent that the large intracavitary tumors which are usually of myxomatous and sometimes sarcomatous structure give rise to a group of symptoms which are quite characteristic. Meroz has pointed out that pedunculated tumors arising in the left heart usually present a clinical picture consisting of palpitation, pain in the cardiac region, edema of the lower limbs, and a degree of dyspnea out of proportion to other physical signs. Of the physical signs, two in particular are emphasized. The first sign, which was pointed out by Ludwig,[22] concerns the production of mitral presystolic murmur. The obstruction of an auriculoventricular orifice by the tumor retards the blood flow, narrows the stream, and produces the auscultatory phenomena of a valvular stenosis.

Ludwig[22] in reporting a case has collected twenty others in which mitral stenosis was diagnosed during life, but at post-mortem examination the obstruction was found to result from the presence of a neoplasm of auricular origin. Several more cases have been reported since.

The second striking feature is the character of the respiratory difficulties described in patients with auricular tumors. It would seem possible that they were produced by the growth mechanically hindering from time to time the

inflow of blood at the entrance of the pulmonary veins, thus producing periods of temporary stagnation in the lung capillaries.

The most characteristic feature is the inability to ascribe a satisfactory etiological cause for the obvious signs of organic heart disease; there is no history of rheumatic fever; digitalis has no effect, and the physical signs may vary in intensity and in character with change of posture, so that in horizontal position only a systolic murmur may be heard, whereas when the patient is erect and the growth tends to sink downwards into the valve orifice a presystolic rumble may be detected. Attacks of intense dyspnea or paroxysms of cyanosis were observed with change of position.

Sudden death is of common occurrence in primary heart tumors, particularly when they arise in the auricle. Death presumably is due to the impaction of the growth in the mitral ring; this ball-valve action effectively obstructs the circulation.

SUMMARY

1. A case of myxoma of the left auricle has been presented in which the diagnosis of mitral stenosis was made ante mortem.

2. Recent advances in intrathoracic surgery have been noted with the implication that the establishment of a symptom complex for early diagnosis of cardiac neoplasm must be obtained.

3. The histology of myxoma and the differentiation of this tumor from organized thrombi are discussed.

4. The pathologic findings suggest that the use of digitalis in this condition may have caused early death of the patient.

5. The hope is expressed that, in cardiac disease suggesting mitral stenosis of unexplained etiology, the diagnostic possibility of a tumor of the left auricle will be considered more frequently.

We wish to thank Dr. Ellis Kellert for the photographs and for other assistance in the preparation of the report.

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ADDENDUM

The complications of mitral stenosis as noted under Reference 10, were listed from the second edition of *Heart Disease* by Dr. Paul D. White. Reference to the third edition shows three other complications that should be added:

1. Pulmonary apoplexy—the result of bleeding from a vessel secondary to the chronic pulmonary hypertension.

2. The frequent occurrence of neurocirculatory asthenia and cardiac neurosis.

3. Hepatic cirrhosis of cardiac origin.

For the sake of completeness and to bring the possible complications of mitral stenosis up to date, these three additional headings are being added.

PAROXYSMAL COMPLETE HEART BLOCK, PRODUCED BY ISCHEMIA OF THE AURICULOVENTRICULAR NODE

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DESPITE our extensive knowledge of conduction in the mammalian heart, the mechanisms that produce intermittent auriculoventricular block in man are not always clear. It is certain that both interruption of the auriculoventricular bundle[1, 2] and vagal impulses[3] can produce conduction disturbances. A hypersensitive carotid sinus,[4] pharyngeal[5] or ocular reflex[6] are clinical examples of the latter. Some difficulties are encountered when these data are applied to paroxysmal complete heart block, a syndrome characterized by periods of auriculoventricular dissociation that alternate with periods during which conduction is normal.

Short episodes of conduction embarrassment have not infrequently been reduplicated by carotid sinus pressure, and their incidence has been reduced by atropine.[7] However, a hypersensitive reflex mechanism, though present, may not come into play in the spontaneous attacks. Many a patient with a sinus sensitive to pressure never has episodes of heart block. If it does, the effect might have been enhanced by lesions in the bundle.[8h] Improvement of

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conduction following atropinization may only mean that a constantly present vagal influence upon the bundle facilitated the development of block; whereas the latter was produced by a factor acting directly upon the auriculoventricular system. Attacks of hours duration can hardly have been produced by nervous influences, that is, if we exclude toxic substances, such as digitalis, from our consideration. They must have an intracardiac basis. It is notoriously difficult to correlate the histologic state of the conduction system with its functional ability during life.[33]

We have examined the thirty-one cases of paroxysmal complete heart block reported in the literature.[8] The block could be temporarily abolished by atropine in six instances.[8c, d, h, p, s] Here the attacks never lasted longer than one to two minutes, usually several seconds. Pressure of the neck produced a short attack of block in one case.[8s] In six cases the conduction system was examined with considerable care.[8e, h, i, k, m, n] In one patient with short attacks of block it was entirely undamaged.[8k] A second case had manifested short attacks of ventricular asystole which were often provoked by swallowing and could be abolished by atropine.[8h] More than two years before death chronic complete block, not abolishable by atropine, became established. A large calcareous mass had breached the continuity of the conduction system at one place. Vagal impulses "playing upon a highly diseased structure"[9] offer an adequate explanation for the attacks. The remaining four cases had shown episodes of complete block lasting from several hours to several months. In all four, inflammatory or degenerative lesions were found in or near the conduction system. In one,[8e] thin-walled blood sinuses had reduced the size of the bundle. In none of these four cases had the continuity of the auriculoventricular connection been breached. In one[8n] atropine failed to improve conduction; in all four, moreover, the duration of the attacks made a nervous influence highly improbable. Increased filling of the sinuses[8e] and temporary pressure by, or edema around, the more permanent lesions have been suggested as the cause of the attacks. In two instances[8i, n] marked narrowing of the small arteries in the vicinity of the conduction system was found. Lewis[8h] suggested that a "disease of the small vessels" might account for the temporary inability of the bundle to conduct impulses.

We shall present a case of paroxysmal complete heart block in which the attacks were produced by ischemia of the auriculoventricular node, diagnosed by the electrocardiogram.

CASE REPORT

E. S., a 76-year-old newspaper artist, was admitted to the Peter Bent Brigham Hospital on April 17, 1944. At the age of 21 years he had had a fainting attack that lasted a few seconds, following an attempt to take something from a high shelf. In 1942 several toes of the right foot had been amputated because of gangrene. Except for some residual pain in the foot, he continued to be entirely well and active. Four weeks before admission the patient started to have attacks of fainting. They occurred while he was standing at work, sitting at home, or lying in bed. They were not related to any position of the head. Sometimes he noticed giddiness before fainting, but mostly the attacks came without warning. They were not associated with biting of the tongue, passing of urine or feces, or convulsions; they lasted for only a few seconds and were followed by no ill feelings. They occurred once to three times a day, but four days before admission he had ten attacks within twelve hours. In one of these he hurt his chin and jaw.

Physical examination showed an active man. His temperature was 98.6° F. (rectal); respirations, 16 per minute; pulse, 60 per minute and regular; and blood pressure 190/80. He showed no cyanosis, edema, dyspnea, or orthopnea. There was tortuosity of the retinal vessels and tortuosity and hardening of the temporal and radial arteries. No pulsations

could be felt over the posterior tibial arteries, and only very weak pulsations could be felt over the dorsalis pedis arteries. The right cheek showed swelling and bluish discoloration and was tender on touch. There were well-healed surgical scars on the right foot. The apical impulse was just palpable. A Grade 3 systolic murmur was heard over the apical and aortic areas. A_2 was diminished in intensity. The lungs were clear.

The red blood cell count was 4,200,000; hematocrit, 37; Hinton, negative; and blood urea nitrogen, 16 mg. per cent. The glucose tolerance test showed a diabetic curve; the urine contained a trace of sugar. A 7-foot film of the heart showed it to be normal in size, by height-weight ratio, and normal in contour. There was calcification in the aortic arch. The lungs were clear.

Clinical Course.—During the first twelve days the patient had twenty-nine episodes of syncope and three of bradycardia. After that no more attacks occurred. In the long syncopal attacks the initial giddiness was followed by unconsciousness and convulsions; during the short ones there were no objective symptoms. Only rarely did the attacks follow excessive torsion of the neck; usually no event could be related to their onset. They frequently happened while the patient was quietly lying in bed. Pulse and heart sounds disappeared with the onset of giddiness and returned at the end of the attack. Six times digital pressure was applied to the left or right carotid sinus, or to both simultaneously. During the first twelve days this invariably resulted in disappearance of pulse and heart sounds and in giddiness or convulsions, after which the original rate was resumed. The syncope could be produced with equal ease whether the ventricular rate prior to pressure was 75, 40, or 20. Later, pressure on the sinus did not produce more than a moderate degree of sinus slowing, confirmed by electrocardiograms.

The three episodes of extreme bradycardia lasted for thirteen, three, and three hours, respectively. In addition to loud and slow heart sounds, rapid and faint sounds were audible. The blood pressure remained unchanged. Weakness and a sick feeling in the stomach were the only complaints. The third attack was preceded and followed by a period of moderately slow rate (40 per minute), lasting for forty-eight and thirty hours, respectively.

Fainting occurred in the course of normal, slow, and intermediate heart rate. Sometimes a rate of 60 before fainting was found to have changed to one of 20 fifteen minutes thereafter; at other times the opposite was the case. We did not observe the heart rate immediately before and after spontaneous syncope. Changes in rate without intervening fainting also occurred.

On both the second and third days the patient received three 0.6 mg. doses of atropine sulfate by mouth; during the following three days this was increased to five 0.6 mg. doses, after which it was discontinued. The drug had no effect upon the incidence of fainting; nor did it prevent the bradycardia from recurring. On the evening of the fourth day, 1.25 mg. injected intravenously failed to increase the pulse rate, which was 25, but only accelerated the auricles from 60 to 75 per minute. However, it abolished, temporarily, the effects of carotid sinus pressure.

The patient was discharged after three weeks. He resumed his work and was last seen in September, 1944. He had been quite well except for an occasional short spell of giddiness, provoked by looking upward. The heart rate was 70; the rhythm was regular.

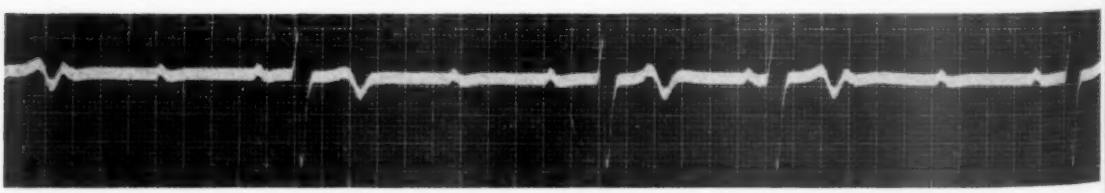

Fig. 1.—Standard Lead II during an episode of bigeminy. For interpretation see text. In this and the following three figures each division of the scale represents 0.04 second (abscissa) and 0.1 millivolt (ordinate).

ANALYSIS OF THE ELECTROCARDIOGRAM

We were able to obtain many electrocardiograms and shall give a detailed discussion of their features. When ventricular rates of 60 to 75 were present, normal sinus rhythm was invariably found. Rates of 40 were due to failure of the ventricle to respond to every second auricular impulse. Rates of 20 to 28

were caused by auriculoventricular dissociation, the auricular rate being 60 to 70. Whenever the ventricle responded to auricular impulses the P-R interval was normal (0.17 second). On the tenth hospital day, occasional coupling was found for a period of three hours. There was complete heart block, but when coupling was present the second complex always represented a sequential beat with a constant and normal P-R interval of 0.17 second (Fig. 1). Two tracings were obtained during carotid sinus pressure, applied when the rate was 70. After initial slowing of the auricles with preservation of the normal P-R interval the ventricular manifestations suddenly disappeared and the auricles speeded up somewhat. Release of pressure was followed by return of unchanged sequential beats at 85 per minute.

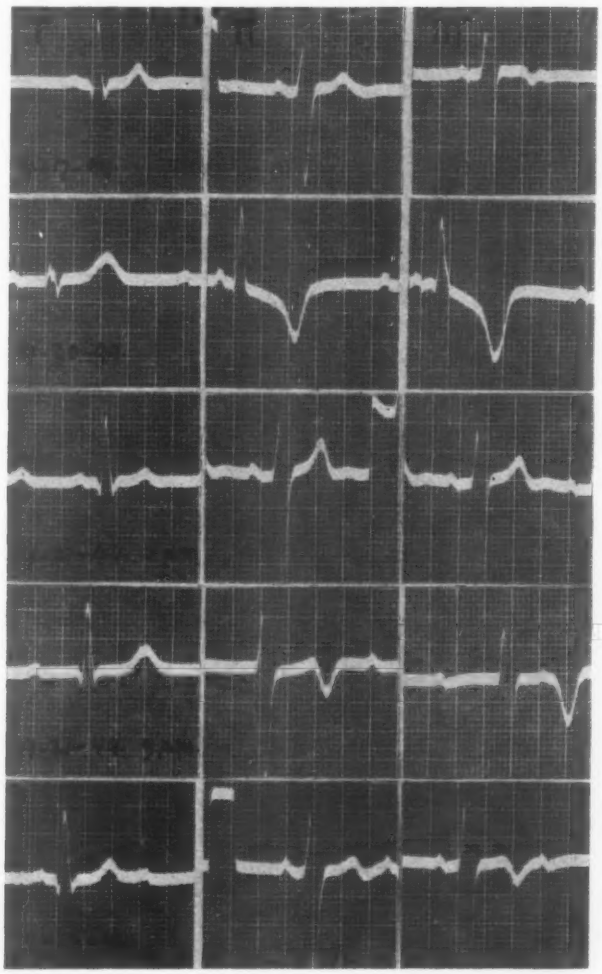

Fig. 2.—Standard leads. First and third rows: normal A-V conduction. Fifth row two-to-one block. Second and fourth rows: A-V dissociation. For interpretation see text.

Two entirely different forms of ventricular complex were found. In the most common one, present on all but one occasion, the initial deflection lasted for 0.14 second (Figs. 2 and 3). It resembles that interpreted by Wilson and his co-workers as right bundle branch block.[10] Unipolar[12] leads were taken from six precordial points[11] and from the three extremities. From Fig. 3 it is evident that we are actually dealing with a block in the right bundle branch. During one of the periods of dissociation a different form of complex was

recorded (Fig. 4). Its duration was 0.12 second. The conduction disturbance is probably in the left bundle branch.

Our main interest is centered upon the final deflection. The marked variability of this part of the ventricular complex is evident from Figs. 2 and 3.* With the purpose of expressing the variations in a quantitative way, a method of analysis has been used that was developed by Wilson and his companions.[13]

Whereas the QRS group is the manifestation of invasion of the ventricular musculature by the electrical process (impulse), the T wave is that of its retreat. The former process occupies a shorter time than the latter. If, however, the duration of complete involvement by the impulse ("electrical systole") is the same for each muscle element of the heart, the electrical effect

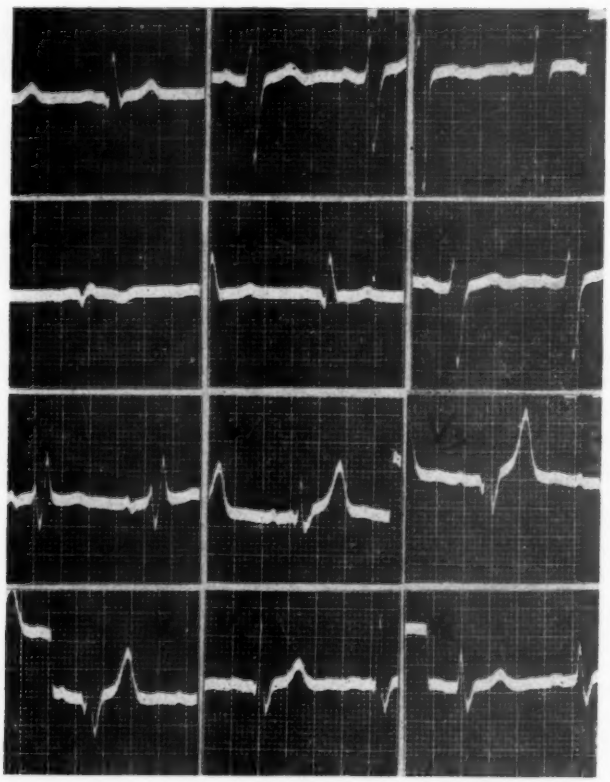

Fig. 3.—Standard leads (first row), unipolar leads from right arm, left arm, and left leg (second row), and unipolar precordial leads from six points during right bundle branch block. The diagnostic features are the double-peaked upward deflection in V_1 and the deep S wave in V_2 to V_6. The unipolar extremity leads are mixtures of the potential changes occurring on the two ventricular surfaces. Normal A-V conduction.

produced by the heart as a whole during invasion will be the same, though opposite in sign, as that during retreat. In that hypothetical case, the areas of QRS and of T, which are a measure of these effects, will also be the same and of opposite sign, and their algebraic sum will be zero. Deviations from this value are a measure of differences in duration of systole of the muscle elements, as projected on the direction of the particular lead. The vector that represents these deviations can be calculated from the areas of the QRS-T complexes of any two standard leads in much the same way as the instantaneous

*The four electrocardiograms that have not been reproduced resemble those of Fig. 2: The electrocardiogram taken on April 22 resembles that taken on April 21 at 2 P.M.; the one taken on April 24 resembles that taken on April 21 at 2 P.M. but has a higher T_2 and T_3; the one taken on April 26 resembles that taken on April 25; and the one taken on April 27 resembles that taken on April 21 at 9 P.M.

electrical axis is obtained. It indicates the direction in which the greatest differences in duration of systole are encountered and points from regions where systole is longest to those where it is shortest. Its size is a measure of the magnitude of these differences. This QRS-T axis has therefore been called "ventricular gradient." It is influenced only by local changes of the ventricular musculature.[13a] The mean axis of QRS and of T, representing, respectively, invasion and retreat during the average moment of these processes, can be calculated in the same way.

All electrocardiograms obtained from our patient were analyzed according to this principle. The practical suggestions of Ashman and Byer[14a] facilitated the measurements of the surfaces. Three complexes were measured in each of the two standard leads of each tracing, and the average was taken as representative value. Deflections above the isoelectric line were considered positive. Any S-T deviations were considered to be part of the final deflection. Proper corrections were made for errors in standardization. The results are tabulated in Table I.

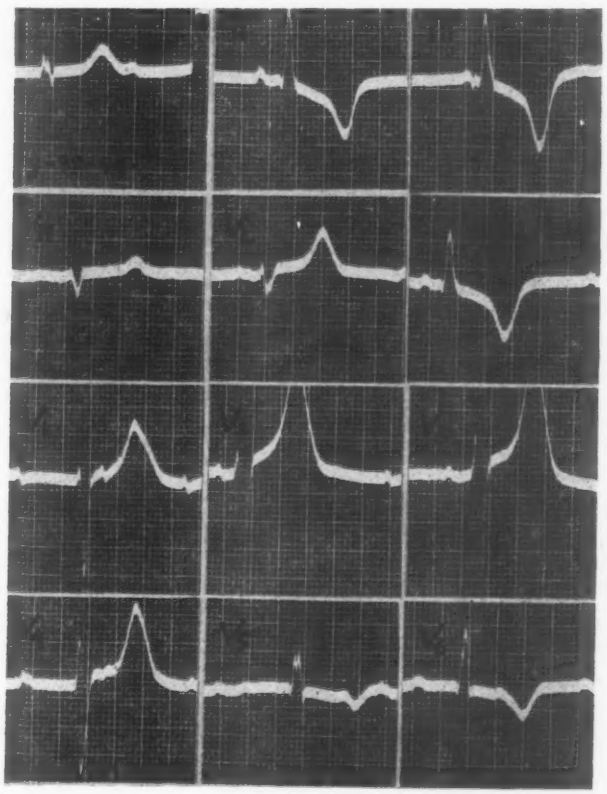

Fig. 4.—Standard leads, unipolar extremity leads, and unipolar precordial leads, probably indicating left bundle branch block. V_1 to V_4 have a normal appearance but are spread out. V_5 shows a bifid R wave. The variations of the right precordium correspond to those of the left arm; those of the left precordium to those of the left leg. A-V dissociation.

INTERPRETATION

Measurements obtained from normal electrocardiograms[14] show that the normal ventricular gradient (A QRS-T) varies from –17 to +86 degrees, and from 2 to 94 microvolt-seconds. The mean axis of QRS (A QRS) varies from –30 to +120 degrees, and from 1 to 50 microvolt-seconds. It should be clear that, if intraventricular block would constitute the only abnormality in the

TABLE I

NUMBER	DATE	VENTRICULAR RATE PER MIN.	A-V CONDUCTION	INTRAVENTRICULAR CONDUCTION	A QRS		A T		A QRS-T (VENTRICULAR GRADIENT)	
					DEGREES	μV-SEC.	DEGREES	μV-SEC.	DEGREES	μV-SEC.
1	4/17/44	55	1:1	R.B.B.B.	−70	80	+39	32	−45	76
2	4/20/44	29	dissociation	L.B.B.B.	+90	52	−75	224	−71	180
3	4/21/44 2 P.M.	70	1:1	R.B.B.B.	−75	92	+74	56	−43	56
4	4/21/44 9 P.M.	24	dissociation	R.B.B.B.	−71	96	−55	68	−65	160
5	4/22/44	65	1:1	R.B.B.B.	−73	96	+74	56	−43	60
6	4/24/44	75	1:1	R.B.B.B.	−75	108	+82	84	−25	48
7	4/25/44	41	2:1	R.B.B.B.	−71	100	+16	24	−59	108
8	4/26/44	43	2:1	R.B.B.B.	−70	80	+30	36	−46	84
9	4/27/44	25*	dissociation	R.B.B.B.	−72	96	−51	68	−63	164
10	8/15/44	70	1:1	R.B.B.B.	−75	60	+39	28	−46	54
11†	3/23/45	67	1:1	R.B.B.B.	−77	76	+51	11	−70	69
12†	3/29/45	22	dissociation	R.B.B.B.(?)	+17	48	−122	256	−113	220
13†	4/ 3/45	35	dissociation	L.B.B.B.	+74	88	−96	272	−89	186

*Coupling was present.
†See Addendum.

ventricles of our patient, the direction and size of the gradient would be within normal limits, whereas the mean axis of QRS would be abnormal. Our data reveal that direction and size of the gradient as well as of A QRS are abnormal in many of the tracings. The ten tracings can be classified in three groups:

I. Tracings 1, 3, 5, 6, and 10. Gradient varying from –25 to –46 degrees, and from 48 to 76 microvolt-seconds. Normal auriculoventricular conduction.

II. Tracings 2, 4, and 9. Gradient varying from –63 to –72 degrees, and from 160 to 192 microvolt-seconds. Auriculoventricular dissociation.

III. Tracings 7 and 8. Gradient –46 and –59 degrees, and 84 and 108 microvolt-seconds. Two-to-one block.

Though of normal size, the gradient has rotated in counterclockwise fashion in the first five tracings. It has increased to approximately three times its usual size and has further rotated in the same direction in the three instances of complete block. The two tracings of two-to-one block have gradients of an intermediate type (Fig. 5). This rotation indicates either the presence of muscle elements that have developed an excessively long electrical systole and are located caudally to those with unchanged electrical properties;

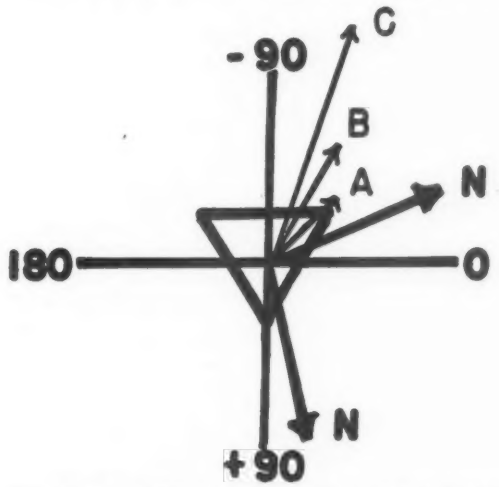

Fig. 5.—Average ventricular gradient during normal auriculoventricular conduction (*A*), during two-to-one block (*B*), and during dissociation (*C*). *N-N* represents the normal range of direction of the gradient.

or the presence of elements with excessively short systole, located cranially to the unchanged ones. It must have been produced by circulatory changes in the heart muscle as they alone would be able to modify local myocardial function. Now it is known that leads taken directly from the borders of an infarcted area show a prolongation of electrical systole.[16] In human patients, this effect, evident in precordial leads, can persist for months and even years. Moreover it is sometimes the only electrocardiographic evidence of an acute myocardial episode. A similar effect appears immediately after occlusion of a coronary artery, before death or severe damage of muscle tissue has had time to develop; it can be abolished by early restoration of the circulation.[15] This change in duration of systole is most pronounced in the superficial, subepicardial, muscle element.[16] Vascular changes do not produce a shortening of systole.

The observed abnormalities must therefore indicate the presence of a long systole in the subepicardial muscle layer of the posterobasal ventricular wall. It is the only evidence of impairment of blood supply to this area and was

present during the four months that the patient was under observation. It might well have existed for a considerable time prior to admission. It is customary to designate the state of musculature which, deprived of its normal blood supply, produces these electrical changes, by the term "ischemia." A similarly located ischemia can be demonstrated in the chronic stage of posterobasal ("posterior") infarction, where it is accompanied by nonresponding (dead) muscle tissue.

The ventricular gradient on three occasions (tracings 2, 4, and 9) gives evidence of a marked increase in ischemia of the posterobasal wall, that was maintained only for a limited number of hours. The additional rotation is similar to that seen in serial curves after posterior myocardial infarction (Bayley[17] and our own observations). The striking growth is a measure of the increase in magnitude of the forces developed late in systole. In many hearts the degree of vascular impairment, of which it is the evidence, would probably have been sufficient to produce electrical manifestations of more advanced damage: elevation of the S-T segment and decrease in size of the T wave.

It will be noted that the gradient is strikingly the same both during the two periods of right bundle branch block and during the period of left bundle branch block, in spite of considerable differences in the mean axis of QRS. It indicates that factors independent of intraventricular conduction were responsible for the acute changes and were acting with equal intensity during either conduction disturbance. The variability among the five tracings with normal auriculoventricular conduction and particularly the changes in the two tracings with two-to-one block are more than is usually found in myocardial disease. These changes are, in principle, of the same nature as those in the instances of dissociation.

We can conceive the acute ischemia as the result of "coronary failure"[18]; that is of a paroxysmal though prolonged disproportion between the blood supply and the demands of the musculature occurring in a region where this supply was already impaired. At no time did the patient complain of angina pectoris. This illustrates the not unusual discrepancy between the degree of vascular impairment and the complaints during life.[18]

During the three periods of acute ischemia the patient also showed complete heart block. It is improbable that the two abnormalities occurred independent of each other. No auriculoventricular dissociation without marked deviation of the ventricular gradient was recorded, and vice versa. It is equally improbable that the bradycardia was responsible for the increase in ischemia of the posterobasal wall. If rates of 25 to 30 would be detrimental to myocardial nutrition, the onset of auriculoventricular block should sometimes coincide with the development of angina pectoris or the aggravation of pre-existing heart pain. We have not seen this and have found no reports in the literature. A patient with hypertension whose idioventricular rhythm gradually slowed from 36 to 7.5 per minute complained of progressive weakness, which ended in unconsciousness, but not of pain. The electrocardiogram failed to show changes in the final deflection.[19*]

The mechanism left to account for the association of the two phenomena is that both were the manifestations of coronary failure. The auriculoventricular connection, especially the node[20] is quite sensitive to diminished oxy-

*It should be understood that the relative adequacy of the coronary circulation during bradycardia does not mean that the development of congestive failure could not be facilitated by that of heart block. The cardiac reserve is determined by more factors than only coronary flow, and might well be insufficient in the face of marked increase in diastolic filling as found in complete block. An example of immediate disappearance of congestive failure with restoration of normal auriculoventricular conduction has been found.[23]

gen supply. Decreasing oxygen concentrations in the inspired air cause progressive auriculoventricular block, ending in dissociation in animals and in man.[21, 22] This occurs in the absence of vagal influences, although vagotomy seems to delay its onset.[21c]

The simultaneous occurrence of both nodal and posterobasal wall ischemia strongly suggests similarities in blood supply to the two structures. In normal hearts the posterobasal wall of the left ventricle usually receives most of its blood from the right coronary artery. Near the beginning of the terminal (descending) part of the vessel the A. septi fibrosi takes its origin, which sends a fine branch to the auriculoventricular node.[24] In only 8 per cent of these hearts the node receives its blood from the left coronary artery.[25] Although sclerosis of the coronary vessels can produce pronounced changes in the distribution of blood,[18] clinical proof of the importance of the identical blood vessel to node and posterobasal musculature of abnormal hearts is found in the association of acute myocardial infarction and heart block. Of the sixty cases (fifty-five with complete and five with second degree block) found in the literature, in which the infarct could be localized with certainty, only eight (13 per cent) had involvement of the anterior (anterolateral) ventricular wall[26] (Table II).

We conclude that, in our patient, chronic ischemia of the posterobasal ventricular wall was present, as shown by the chronic counterclockwise deviation of the ventricular gradient; that during the episodes of heart block this ischemia increased markedly, as shown by additional rotation and growth of the gradient; and that coincidentally with this an ischemia of the auriculoventricular node developed which resulted in inability of this structure to conduct impulses; both nodal and myocardial ischemia probably being produced by failure of the same artery.

Microscopic changes in the posterobasal wall would not necessarily have been found. From our own observations we noticed that such changes are not infrequently lacking in instances of acute or chronic T-wave inversion, and even in instances of elevation of the S-T segment.

The electrocardiogram reproduced in Fig. 1 shows that the ventricular gradient during the sequential beat was the same as that during the idioventricular beats. Although the reason for the temporary improvement in conduction is not clear (a supernormal phase[27] is highly improbable as it would require a P-R interval of 0.9 second), the functional change did not apparently involve a large part of the musculature.

Carotid sinus pressure never resulted in the development of an independent ventricular rhythm but simply suppressed all ventricular activity. This was also observed in the instances where complete heart block had been present previous to the application of pressure. From this we may conclude that the block was localized in the auriculoventricular node and that vagal influences were not responsible for the establishment of auriculoventricular dissociation. The latter is confirmed by our inability to improve conduction with intravenous atropine and by the long duration of the periods of dissociation. On the other hand some of the attacks of giddiness or unconsciousness

TABLE II

POSTERIOR INFARCTION PROVED BY				ANTERIOR INFARCTION PROVED BY			
ECG	P.M.*	BOTH	TOTAL	ECG	P.M.*	BOTH	TOTAL
34	4	14	52	2	3	3	8

*The post-mortem evidence refers to the finding of massive myocardial involvement.

might well have been due to changes in the degree of block, whereas others undoubtedly were of vagal origin.

It is interesting that carotid sinus pressure failed to produce ventricular asystole as soon as the attacks of heart block stopped. Whereas we are at a loss to explain why the latter failed to return, it is hard to avoid the conclusion that the sensitivity of the reflex mechanism was mainly due to changes in the auriculoventricular node or in the vagal endings around it. A moderate degree of ischemia, not enough to impair conduction, might well have been responsible for it.

DISCUSSION

Except for the cases of myocardial infarction, clinical instances of auriculoventricular block due to deficient oxygen supply to the conduction system are few in number and little convincing. Barach and Woodwell[28] described a case of rheumatic heart disease, hypertension, and advanced congestive failure. Delayed auriculoventricular conduction and right bundle branch block were present. Oxygen administration for one-half hour resulted in decrease of cyanosis and "absence of the marked auriculoventricular block" for at least one-half hour. McCulloch[29] reported two instances of prolongation of the P-R interval in babies in whom vomiting and diarrhea had resulted in marked dehydration. After improvement the P-R interval returned to normal. Gager[30] found a prolonged P-R interval in a patient with a pericardial effusion. This disappeared after 500 c.c. of sterile fluid had been removed.

The effect of nitrites has been investigated in two instances. Wolferth and McMillan[8n] were unable to improve conduction with amyl nitrite in a case of paroxysmal heart block. On the contrary the block increased, due to acceleration of the auricles. Lawrence and Forbes[8y] report a case of paroxysmal dissociation. The attacks sometimes lasted for several hours. Inhalation of amyl nitrite invariably abolished the block: normal rhythm with normal P-R interval became established within two minutes and persisted for one-half hour. There was no difference between the final deflection of the sequential beat and that of the idioventricular beat (only the "right pectoral lead" is available for comparison). Gross examination of the heart showed no change in the bundle or any part of the myocardium. There were small atheromatous plaques throughout the coronary arteries, not enough to obstruct the lumen at any point.

The combination of angina pectoris and auriculoventricular block is also rare. Campbell[8x] mentioned a case in which Stokes-Adams attacks started with severe precordial pain, radiating up the left side to the lower angle of the jaw. Gallavardin[31] reported three cases in which syncope sometimes was preceded by chest pain. No observations of any kind were made during the attacks. A more convincing report is that of Gallavardin and Rougier.[32] A patient with angina pectoris had a prolonged attack of pain. For a month thereafter each attack was followed by syncope and convulsions. The electrocardiograms during these attacks showed auriculoventricular dissociation; between the episodes conduction occurred without delay.

Pathologic evidence of the importance of an adequate blood supply to the node for auriculoventricular conduction is found in two papers by Géraudel.[33a, c] He carefully examined the hearts of two patients with chronic complete block plus Stokes-Adams attacks and chronic first degree block with attacks of dissociation, respectively. In both cases a normal node and bundle were found, but there was marked narrowing and obstruction of the A. septi fibrosi and of other small arteries.

We have looked for cases of paroxysmal complete heart block associated with growth and counterclockwise rotation of the ventricular gradient, but we found no case comparable to our own. Parkinson, Papp, and Evans[34] reported a case of chronic complete block with attacks of ventricular asystole. The electrocardiogram showed right bundle branch block and very deep T_2 and T_3 waves; this is the only instance of its sort. Levine and Matton[35] reported ventricular fibrillation which lasted for 3.5 minutes and was followed by a period of ventricular asystole of 1.3 minutes in a patient with chronic auriculoventricular dissociation. She recovered after intracardiac adrenalin. The ventricular gradient before the attack was of normal size and pointed to the left and slightly upward. T_2 and T_3 were inverted. After the attack the gradient had markedly increased in size and had rotated in counterclockwise direction; T_2 and T_3 were more deeply inverted.

The rarity of posterior wall ischemia in chronic and paroxysmal heart block must be ascribed to the size of the lesion which, even when of vascular origin, needs not involve any muscle tissue to cause interruption of the auriculoventricular connection.

SUMMARY AND CONCLUSIONS

A case of paroxysmal auriculoventricular dissociation in a 76-year-old man was described. The three periods of complete block that were observed lasted for thirteen, three, and three hours, respectively. Atropine by mouth and intravenously failed to improve conduction. Pressure on either carotid sinus, applied between attacks, produced ventricular asystole resulting in syncope and convulsions without the development of an idioventricular rhythm. The reflex sensitivity could be abolished by atropine and was undoubtedly responsible for several of the fainting attacks of which the patient complained. These attacks disappeared after the twelfth day of his hospital stay as did also the carotid sinus sensitivity and the episodes of dissociation.

Simultaneously with the dissociation marked changes developed in the final ventricular deflection of the electrocardiogram, which disappeared when conduction again became normal. By determining the ventricular gradient it was found that a severe ischemia of the posterobasal ventricular wall had produced them. A moderate degree of ischemia of the same part of the heart muscle was present during normal conduction for the four months that the patient was under observation.

As it was considered improbable that the bradycardia was the cause of the abnormal state of the musculature it was concluded that both the paroxysmal changes in the final deflection and the simultaneous development of complete heart block were due to coronary failure, resulting in ischemia of the posterobasal ventricular wall and the auriculoventricular node, respectively.

We are grateful to Dr. S. A. Levine, who read the manuscript and made several suggestions.

Addendum.—The patient was readmitted on March 19, 1945, because of increasing pain in his right foot. A film of the foot showed extensive osteomyelitis of the tarsal bones. With rest in bed the pain diminished markedly. On the eleventh hospital day he began to have syncopal attacks and convulsions, during which no pulse could be felt. Between the attacks a pulse rate of 22 to 40 was found, whereas it had been 65 to 80 before this period. Eight convulsive episodes occurred in the course of four hours. Then the pulse rate rose to 70, and the patient was again well. When he was allowed to get up, four days later, the attacks recurred, and continued, often with intervals of only a few minutes, for twenty-four hours. Adrenalin and atropine were ineffective. At the end of this period the patient expired in an episode of asystole.

An electrocardiogram obtained three days after his admission differed from the one taken in September, 1944, in that T_1, T_2, and T_3 were very flat. Consequently the ventricular gradient is similar to the mean axis of QRS (Number 11, Table I). A tracing obtained during a period of bradycardia between convulsions (eleventh hospital day) showed complete auriculoventricular block. The ventricular complexes were wide (0.16 second) and, because of the presence of a deep Q_1, were probably indicative of right bundle branch block. (No precordial leads were taken.) The electrocardiogram taken several hours before death also showed dissociation. The wide (0.14 second) complexes, consisting of a single upward deflection, indicated left bundle branch block.

In spite of great differences in direction and size of A QRS the gradients obtained from the latter two tracings closely resemble each other (Numbers 12 and 13, Table I). As compared with those during previous episodes of dissociation, a rotation to the left and an increase in size have occurred, indicating a more severe (and more extensive) ischemia of the posterobasal wall.

The heart weighed 420 grams. There were some dilatation of the left ventricle and a moderate increase in thickness of the left ventricular wall. No areas of infarction or scarring were seen. Although the coronary arteries were markedly tortuous and calcified, with many atheromatous plaques, no occlusions of the lumina were found. The region of the auriculoventricular conduction system showed no abnormalities. The margins of the aortic cusps were calcified and thickened.

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THE TREATMENT OF AURICULAR FIBRILLATION OCCURRING WITH MYOCARDIAL INFARCTION

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AURICULAR fibrillation occurs as a complication of myocardial infarction in about one in twelve cases[1-4] (8.3 per cent). No definite criteria have been agreed upon as to its management. It has been regarded by some as usually transient and by others as not apparently altering the prognosis. Any increase of mortality has been ascribed to the associated heart failure or shock, rather than to the arrhythmia. Digitalis and quinidine administration often have been regarded as dangerous and to be considered only as a late, not an early, procedure in treatment.

As a result of varying opinion, one never is quite sure, when auricular fibrillation appears with myocardial infarction, whether to view the arrhythmia expectantly, hoping it will prove to be transitory; whether to ignore it completely, assuming that it will not alter the prognosis anyway; or whether to treat it medically and accept a quantitatively unknown risk from the use of drugs. If one decides to treat it medically, there is uncertainty as to the method of treatment. Should digitalis or quinidine, or both, be used? How soon, how much, and how often? What are the hazards to anticipate as the result of this therapy? These questions arise, and there have been no uniform answers. This is undoubtedly due to the relative infrequency of the arrhythmia which has prevented an adequate analysis of a large series.

In a previous study of eighty-four patients with auricular fibrillation complicating myocardial infarction,[4] it was found that in the majority the arrhythmia persisted, that the prognosis was worse in the group with persistent auricular fibrillation, and that the prognosis was worse due to the effects of the arrhythmia itself, and not alone to the associated heart damage. It was concluded that an early attempt to eliminate the arrhythmia was indicated unless the risk of the drug used was greater than the risk of the continuance of the arrhythmia. It was found that if congestive failure was associated with the arrhythmia, the use of digitalis alone was apparently harmful, due to production of fatal emboli to the greater circulation. This was tentatively ascribed to several factors, of which persistence of the arrhythmia plus production of an increased constricting expulsive effect upon the ventricle seemed most important.

This is a further clinical statistical study of the data in an attempt to establish tentative positive criteria for treatment. This paper is a study of the results of treatment of these eighty-four patients with auricular fibrillation occurring in 1,247 patients with myocardial infarction admitted to the Los Angeles County General Hospital. We have tried to evaluate the risk of the drug treatment against the natural risk of the condition. Only patients with characteristic electrocardiograms were accepted. Of the eighty-four, seventeen received no medication. The results in these cases served as a control series in indicating the natural course and natural risks in untreated cases. We tried to measure the beneficial effects versus the harmful effects of digitalis and quinidine. The

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primary beneficial objective effects to be obtained in auricular fibrillation from digitalis and quinidine administration were considered as a slower, stronger, ventricular systole and a return of an irregular ectopic rhythm to a regular sinus rhythm. These beneficial effects should be reflected and measurable in an improvement of the mortality rate. The theoretical risks are those of sudden death, embolism, and rupture, and can be determined objectively. The best treatment should be shown, therefore, by a low mortality rate, a high percentage of return to sinus rhythm, and no greater risk of sudden death, embolism, or rupture from the drug than the natural risk from the condition itself.

SUDDEN DEATH AND RUPTURE OF THE HEART

There was no evidence that digitalis increased the mortality by increasing the incidence of sudden death. Quinidine apparently caused three cases of sudden death, but all three were patients with obvious conduction defects, conditions in which the drug should not ordinarily be given (Table I). Rupture of the heart occurred in three of fifty-six patients given digitalis or digitalis and quinidine (5.3 per cent). One patient in seventeen given no medication developed cardiac rupture (5.8 per cent). Rupture of the heart apparently was not a drug hazard in our series.

TABLE I. SUDDEN DEATH OCCURRING IN PATIENTS WITH MYOCARDIAL INFARCTION PLUS AURICULAR FIBRILLATION

TYPE OF MEDICATION	NUMBER OF PATIENTS	NUMBER DYING SUDDENLY	PER CENT
Digitalis alone	44	7	15.9
No digitalis or quinidine	17	3	17.6
Quinidine alone	11	3	27.2
Both digitalis and quinidine	12	0	0
Total	84	13	15.4

MATERIAL

The eighty-four patients, as a group, first were studied as to response to varying medications and to no medication (Table II). The response of the thirty-six patients without congestive failure (Table III) and the forty-eight patients with congestive failure was then determined (Table IV). In order to be sure that congestive heart failure and not peripheral circulatory failure was being treated, only those with objective findings of liver enlargement and ankle edema were included in the congestive failure group.

ADMINISTRATION OF QUINIDINE AND DIGITALIS

The size of the dose of the quinidine and the time interval between doses varied considerably, as the patients were under the care of many different doctors. An average dose was 15 to 20 grains in twenty-four hours. The dose varied from 3 to 6 grains, and the time interval varied from 2 to 6 hours. Thus in very few instances was an optimum effect of quinidine obtained such as would result from a regular administration at 2- to 3-hour intervals. Digitalis was given in no uniform fashion. In the patients with congestive failure, a frequent method of administration was to give the 3 grains of powdered leaf after meals for two to three days. Most of the patients received 20 to 30 grains in three to four days. It is probable that an optimum digitalis effect was obtained in more instances than was an optimum quinidine effect. In most instances no medication was begun until the auricular fibrillation had lasted twenty-four hours or more.

RESULTS

1. *The Group of Eighty-Four as a Whole (Table II).*—Quinidine alone gave the best results, with the lowest mortality and the highest percentage of return to sinus rhythm.

TABLE II. EFFECT OF MEDICATION IN 84 PATIENTS WITH AURICULAR FIBRILLATION AND MYOCARDIAL INFARCTION

(Mortality in Relation to Return to Sinus Rhythm and Incidence of Embolism)

	NUMBER	AURICULAR FIBRILLATION STOPPED	PERCENTAGE RETURNED TO SINUS RHYTHM	NUMBER SYSTEMIC EMBOLI	NUMBER OF DEATHS	MORTALITY (%)	PERCENTAGE OF DEATHS DUE TO EMBOLI
Quinidine alone	11	9	82	0	6	54.5	0
Digitalis plus quinidine	12	9	75	1	8	67	12.5
No medication	17	5	29	2	12	71	17
Digitalis alone	44	6	14	14	41	93	34

2. *The Group of Thirty-Six Without Congestive Failure (Table III).*—Quinidine alone gave the best results, with an equally high percentage of return to sinus rhythm as when quinidine and digitalis were given and the lowest mortality despite three possibly avoidable deaths occurring when quinidine was given to patients with obvious conduction defects. The patients receiving digitalis alone had a smaller percentage of return to sinus rhythm and a higher mortality rate than the patients receiving no medication.

TABLE III. RESULTS OF MEDICATION IN THIRTY-SIX PATIENTS WITH MYOCARDIAL INFARCTION AND AURICULAR FIBRILLATION BUT NO CONGESTIVE FAILURE

	NUMBER	AURICULAR FIBRILLATION STOPPED	PERCENTAGE RETURNED TO SINUS RHYTHM	NUMBER SYSTEMIC EMBOLI	NUMBER DIED	MORTALITY (%)	SUDDEN DEATH (%)
Digitalis and quinidine	5	4	80	1	4	80	0
No medication	9	5	55	2	6	66.6	1 (16)
Digitalis alone	12	3	25	1	9	75	1 (11)
Quinidine alone	10	8	80	0	5	50	3 (60)
Total	36	8	55	4	24	66	

3. *The Group With Congestive Failure (Table IV).*—Of eighty-four patients with congestive failure in addition to the arrhythmia, there were the following findings:

a. If no medication was given, none returned to sinus rhythm, 75 per cent died; none had clinically recognized systemic embolism, but half of the deaths were sudden.

b. If digitalis alone was given only 9 per cent returned to sinus rhythm, 96 per cent died; 41 per cent died of clinically recognized systemic embolism, and 19 per cent of the deaths were sudden.

TABLE IV. RESULTS OF MEDICATION IN FORTY-EIGHT PATIENTS WITH MYOCARDIAL INFARCTION, AURICULAR FIBRILLATION, AND CONGESTIVE FAILURE

	NUMBER	AURICULAR FIBRILLATION STOPPED	PERCENTAGE RETURNED TO SINUS RHYTHM	NUMBER SYSTEMIC EMBOLI	NUMBER DIED	MORTALITY (%)	SUDDEN DEATH (%)
Digitalis and quinidine	7	5	70	0	4	59	0
No medication	8	0	0	0	6	75	3 (50)
Digitalis alone	32	3	9.3	13	31	96.8	6 (19)
Quinidine alone	1	1	100	0	1	100	0
Total	48	9	18.7	13	42	80.7	

c. If digitalis plus quinidine was given, 70 per cent returned to sinus rhythm, 59 per cent died; none had systemic embolism, and none died suddenly. The single patient treated with quinidine alone can be excluded.

SUMMARY OF FINDINGS

1. Digitalis administration did not induce sudden death or cardiac rupture in a significantly higher percentage than no medication.

2. Digitalis was apparently harmful when given alone in both the group with congestive failure and the group without congestive failure.

3. Digitalis alone was harmful apparently because it prevented a spontaneous return to sinus rhythm in the group without congestive failure, and because it induced fatal systemic emboli in the group with congestive failure.

4. Quinidine alone was harmful only when given in the presence of obvious conduction defects.

5. Sudden death could not be correlated with the use of either drug save in the three cases with obvious conduction defects.

6. Although sudden death occurred if no medication was given, or if digitalis alone or quinidine alone was given, it occurred in none of the twelve patients given both digitalis and quinidine.

7. In the group with no congestive failure, quinidine alone gave better results than no medication or digitalis alone.

8. In the group with congestive failure (excluding the single case given quinidine alone) the worst results were from digitalis alone. Thirty-one of the thirty-two patients died (96.8 per cent).

Thirteen of these were due to emboli to the greater circulation. The best results were from combined digitalis and quinidine. In this group there was the lowest mortality, the greatest percentage of return to sinus rhythm, and no sudden deaths from embolism.

DIGITALIS AND QUINIDINE

Theoretically digitalis and quinidine should act as buffers against each other's action tending to induce an ectopic ventricular rhythm. Digitalis is capable of inducing paroxysmal ventricular tachycardia, an arrhythmia which quinidine can prevent; conversely, digitalis is believed to prevent ventricular tachycardia arising from the use of quinidine in the treatment of auricular fibrillation. This reciprocal effect may or may not have been responsible for the absence of sudden death in any of the twelve patients who received both digitalis and quinidine.

DISCUSSION

It is fallacious to generalize from a statistical analysis of a numerically small group. The group studied is numerically small. It represents a group culled from many years of admissions to a large general hospital, however, and establishes some deductions referable to this group which may or may not prove to be generally true. Certain deductions seem fairly obvious. Quinidine alone should not have been given to the patients with obvious conduction defects. This contraindication is generally recognized. Digitalis alone apparently should not have been given to the patients with congestive failure. The incidence of fatal emboli associated with the use of digitalis alone in the patients with congestive failure was too high to be explained upon the basis of chance alone. Early elimination of the auricular fibrillation would have been advisable in view of the correlation of the increased incidence of fatal systemic emboli with

the prolongation of the arrhythmia. The longer the auricular fibrillation was allowed to persist, the greater became the hazard of embolism. The risk of embolism apparently was not in reverting the auricular fibrillation to sinus rhythm but in allowing the auricular fibrillation to persist. The duration of the auricular fibrillation seemed to be related directly to the tendency to fatal emboli. Of eight patients with known pre-existent auricular fibrillation, seven died, of whom five died from emboli to the greater circulation. Of thirty-six patients who had auricular fibrillation at the onset of the attack and who died within seven days with persistent auricular fibrillation, only seven died of fatal emboli. But of thirteen patients in whom the auricular fibrillation persisted over seven days, nine died of fatal systemic emboli. The practical problem of treatment in this whole group of 84 was the treatment of those 49 patients in whom auricular fibrillation was found in the first electrocardiogam, and presumably developed the arrhythmia coincident with the attack. Only two of these forty-nine reverted to sinus rhythm, and forty-two of forty-nine died (85.7 per cent). There was no particular problem in the treatment of those patients who developed auricular fibrillation definitely after the attack. In these patients, the arrhythmia was usually transient and the mortality only slightly increased. Usually no congestive failure was present, and quinidine alone gave the best results (Table III). Of thirty-five patients who developed auricular fibrillation definitely after the attack, only eight persisted in the arrhythmia. In six of the thirty-five patients no medication was given, and in four of those six the arrhythmia disappeared in twenty-four hours. In the absence of congestive failure, it would seem permissible to wait twenty-four hours to see if the arrhythmia is transient. The group of patients in whom the auricular fibrillation was found in the first electrocardiogram, however, usually had had severe previous cardiovascular disease, and a large percentage had congestive failure. Theoretically, treatment directed at elimination of the arrhythmia as well as improvement of the ventricular systole should give the best results. This should be accomplished by giving both quinidine, to revert the ectopic rhythm to sinus rhythm, and digitalis, unless the dangers of the drugs are greater than the danger of the continuing arrhythmia. The risks of quinidine and digitalis given together in this series were less than the risks of no medication. Where they were given together for congestive failure, sinus rhythm returned in a high percentage, and the mortality was low (59 per cent). The group is small but corroborates the theoretical prediction. Therefore, we believe that both digitalis and quinidine should have been given immediately when auricular fibrillation was found in the first electrocardiogram if congestive failure was present. Our data show that if digitalis alone was given, the mortality was 97 per cent. If there was no medication, the mortality was 75 per cent; but if both digitalis and quinidine were given, it was 59 per cent. The use of quinidine in congestive failure ordinarily is considered contraindicated. In the congestive failure associated with auricular fibrillation in myocardial infarction, however, it would seem especially to be indicated for the following reasons: Factually, (1) digitalis alone proved to be dangerous; it increased, rather than decreased mortality; and (2) digitalis plus quinidine proved to be superior; and theoretically, (3) a quick return to sinus rhythm should: (a) prevent further auricular thrombus formation and forestall embolism, and (b) reduce the ventricular rate after the usual initial acceleration.

What other measures may be justifiable in such a desperate situation with 97 per cent mortality, that is, auricular fibrillation and congestive failure occurring in the early days of the infarction (?). Auricular anoxemia and vagal

activity seem to be the factors involved in the production of the arrhythmia in the experimental animal.[5] In addition to oxygen to relieve anoxemia, the use of atropine as an adjuvant to quinidine may well be considered. Lewis[6] says the end result of both atropine and quinidine are the same in their action toward auricular fibrillation, only that atropine has a far less powerful effect. They both depress vagal activity, tend to prolong the refractory period, and depress the auricular rate.

LeRoy and Snider,[7] Falk,[8] Gilbert,[9] and Rathe[3] already have strongly advocated atropine in myocardial infarction to counteract reflex vasospasm acting through the vagus.

Korns[10] believes it deserves an extended clinical trial because of this action alone. For the auricular fibrillation occurring synchronously with the onset of myocardial infarction where the mortality is nearly 100 per cent, a dual beneficial action would be welcomed. Atropine would seem to deserve a trial here, too.

THE PROGRAM OF MEDICATION

As a result of these data, our general scheme of management of auricular fibrillation occurring with myocardial infarction in the future will be that of an immediate attempt to stop the arrhythmia by the administration of optimum doses of quinidine unless (A) the electrocardiogram shows conduction defects or (B) the arrhythmia occurs several days after the onset of myocardial infarction, and no congestive failure is present. In the latter instance we should wait twenty-four hours to see if there is a spontaneous return to sinus rhythm. If congestive failure is present both quinidine and digitalis will be given at once. Quinidine will be given every two hours in 6-grain doses if there is no hypersensitivity to the initial 3-grain dose. The administration of digitalis alone in such cases will be especially avoided, as we feel it is contraindicated. If auricular fibrillation occurs coincidentally with the attack of myocardial infarction, in addition, we shall give atropine sulfate in an initial dose of $\frac{1}{50}$ grain (1.3 mg.) intravenously and follow by $\frac{1}{150}$ grain (0.5 mg.) by mouth three times daily. These measures seem rational. Only clinical statistical data can prove their value.

SUMMARY AND CONCLUSIONS

1. Auricular fibrillation occurring with myocardial infarction in eighty-four patients represented a definite hazard if allowed to continue.

2. Digitalis alone was apparently harmful whether used in patients with or without congestive failure.

3. Digitalis and quinidine together gave the best result when used in patients with congestive failure plus auricular fibrillation. This was based upon the criteria of mortality rate, return to sinus rhythm, and incidence of occurrence of embolism, rupture, or sudden death.

4. Quinidine alone was adequate if no congestive failure was present.

5. If these data apply generally, digitalis alone should not be given for auricular fibrillation occurring with myocardial infarction. Quinidine plus digitalis should be preferable.

6. A tentative program for medication is suggested.

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THE VALUE OF LEAD IVF IN CARDIAC INFARCTION

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IN THE past, the three standard limb leads frequently have proved inadequate when electrocardiographic confirmation of a clinical diagnosis of cardiac infarction was desired. This led Wolferth and Wood[1] to add the anteroposterior chest lead to the electrocardiogram in an attempt to increase its diagnostic value in this condition.

Normal values for the potential variations in chest leads were later established by Hoffman and DeLong,[2] Katz and Kissin,[3] Goldbloom,[4] Master,[5] Rosenblum and Sampson,[6] Shipley and Hallaran,[7] and Sorsky and Wood.[8] To standardize the information obtained from various sources, a Joint Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland was appointed. The recommendation of this Committee[9] that, if a single precordial lead be done, Lead IVF (apex-left leg) be the derivation of preference, has been followed at the Toronto General Hospital since Jan. 1, 1938.

Many investigators have emphasized the fact that multiple chest leads are essential to complete electrocardiographic examination of the heart. No single precordial derivation will give the maximum information in all forms of heart disease. However, as a matter of routine in practice, it is seldom feasible to record more than four or, at the most, five leads in a single electrocardiogram. Most routine electrocardiograms of recent years consist of the standard limb leads and Lead IVF. It should be kept in mind that this chest lead was recommended chiefly for its value in anterior cardiac infarction and that other precordial derivations may contribute to the diagnosis of other cardiac conditions much more fully than Lead IVF.

The characteristic changes in chest leads in serial records of cases of recent infarction of the anterior wall of the myocardium have been described in detail.[1-3, 10-20] Since changes in the QRS complex in Lead IVF are important in the differential diagnosis of infarction from other forms of heart disease, a review of QRS complexes in CF leads in normal hearts may bring abnormal findings into sharper focus* (Fig. 1).

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* In CF_4 the precordial electrode is placed in the fifth left intercostal space in the midclavicular line irrespective of the size or position of the heart, whereas in IVF the electrode is placed on the outer border of the cardiac apex.

QRS Complex in Normal CF Leads.—As the chest electrode travels from CF_1 to CF_4, i.e., from the right border of the sternum in the fourth intercostal space to the left midclavicular line in the fifth intercostal space and thence, at this same horizontal level, to the anterior axillary line (CF_5) and midaxillary line (CF_6), the QRS complex goes through the changes outlined in Fig. 1. The small initial upward deflection (R) present in CF_1 rises progressively so that,

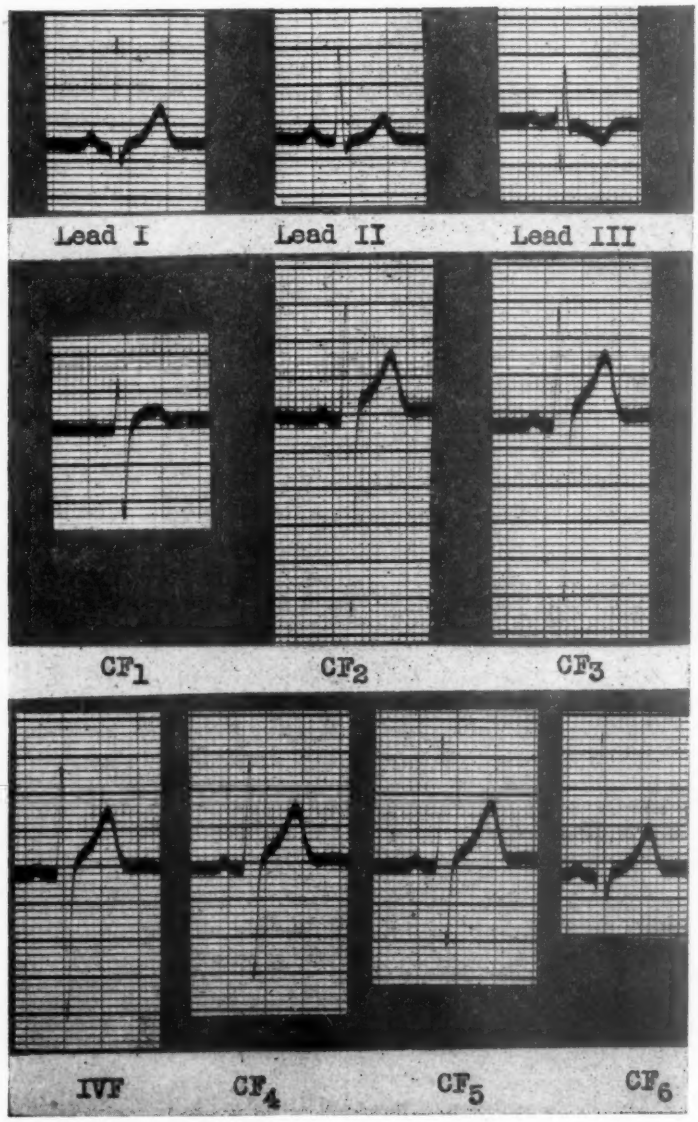
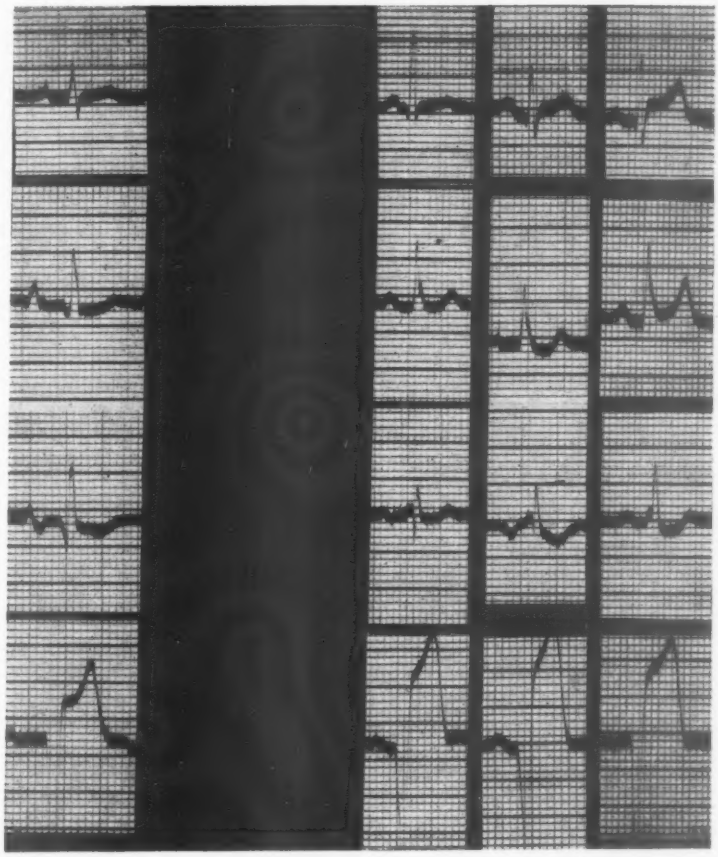


Fig. 1.—The standard limb leads and CF derivations from a young man with no evidence of heart disease.

in CF_4, R and S waves are usually about equal in magnitude. Farther to the left, the R wave remains high while there is a progressive diminution in the depth of the S wave until the latter may disappear entirely. Usually just before the S wave disappears an initial negative deflection (Q) develops; this deflection is seldom greater than 1 to 2 mm. in depth.

In the presence of recent infarction of the anterior wall of the myocardium, the initial QRS deflection in Lead IVF usually becomes negative (development

of a Q_4) associated with a marked reduction or complete disappearance of the R wave. The S wave remains a deeply negative deflection so that QRS_4 usually becomes wholly negative (Figs. 2 to 7). Less frequently R_4 remains the initial QRS deflection. When this occurs, R_4 is usually small, under 2 mm. in height, but may be somewhat higher or even of normal height (Figs. 4, *b*, *c*, *d*, and *e*). Early in the course of the infarction the RS-T segment is markedly elevated, giving place, in a few days, to a negative T wave of symmetrical limbs, which may become very deeply negative (Fig. 5, *f*).



a. *b.* *c.*

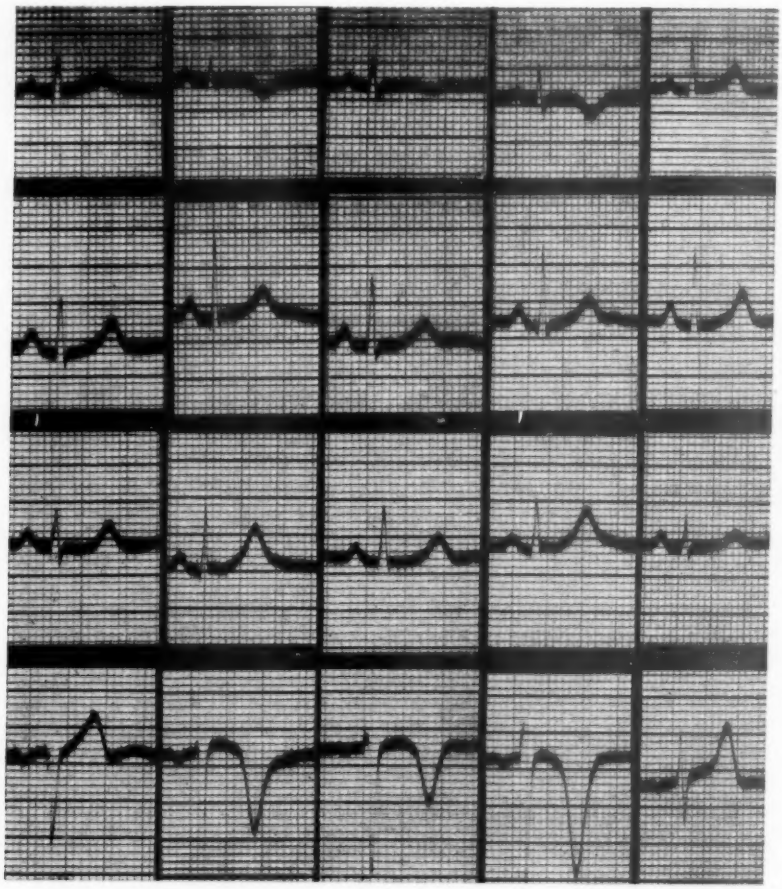
Fig. 2. Fig. 3.

Fig. 2.—W.B., Feb. 16, 1940. Angina pectoris for one year. Prolonged pain Feb. 7, 1940. A good example of the value of Lead IVF in the diagnosis of recent anterior infarction (confirmed at autopsy Feb. 19, 1940) in the only record obtained. While there is slight depression of the RT segment in Lead III, there is no finding in Lead I that would contribute to the diagnosis.

Fig. 3.—G.H., June 27, 28, and 29, 1940. Angina pectoris for one year. Prolonged pain June 24, 1940. The diagnosis of recent anterior infarction in the initial record depends entirely on the Lead IVF findings of marked elevation of the RT segment associated with absence of the R wave. The diagnosis is obvious in the limb leads in the second and third records. (Diagnosis confirmed at autopsy June 30, 1940.)

Usually, in anterior infarction, in the presence of an entirely negative QRS complex in IVF, a notching of the descending limb can be seen (Fig. 4, *a*). According to Mortensen,[14] this represents the remnant of the R wave which has been reduced to this degree. This notch may be of value in helping to differentiate anterior infarction and left ventricular hypertrophy which, rarely, may be responsible for the absence of the R wave in CF_4. When this does occur, no semblance of R_4 remains.

Since the development of a Q wave in Lead IVF is important to the diagnosis of anterior infarction, it occasionally becomes necessary to distinguish between a normal and an abnormal Q wave. A normal Q wave (less than 2 mm.) is usually associated with a high R wave and a small or absent S wave (Fig. 1). In the CF_4 position this may obtain normally with a small, centrally placed heart. On the other hand, the Q wave of anterior infarction usually is accompanied by marked reduction in the height of R_4 while the S wave remains deeply negative.



a. *b.* *c.* *d.* *e.*

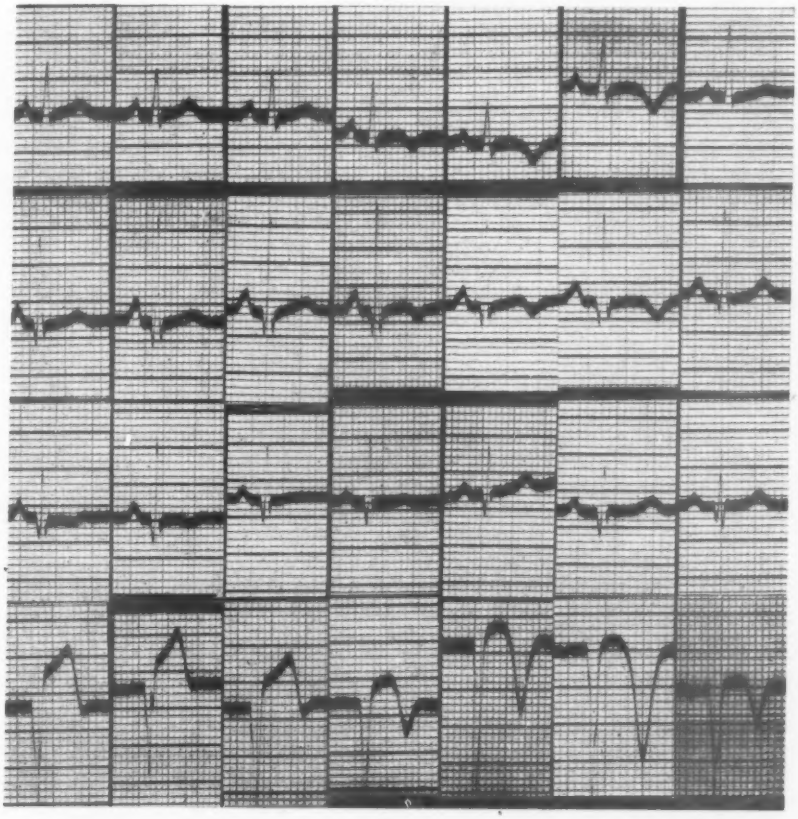
Fig. 4.—P.G., Jan. 12, 13, 17, and 31, 1939, and Feb. 21, 1940. Angina pectoris for two years. Prolonged attack Jan. 12, 1939. The sole diagnostic feature of the initial record is the absence of the R wave in Lead IVF, although there is suggestive depression of the RT segment in Lead III. The diagnosis is obvious in both limb leads and in Lead IVF in the next three records made during the three weeks following the attack of prolonged pain. Complete reversion to a normal record has taken place one year later. (See follow-up group.) At postmortem examination (Aug. 23, 1940) fibrosis in the apex of the left ventricle was found.

MATERIAL

All cases of cardiac infarction admitted to the public wards of the Toronto General Hospital in a four-year period, 1938 to 1941, have been reviewed. Electrocardiographic records were made at frequent intervals on the majority of cases of recent infarction. In addition to the study of cases of cardiac infarction, all records showing abnormalities in the ventricular complex were reviewed. This latter study was confined to the first thirty months of the four-year admission period, and only the records of those cases coming to autopsy

were selected for analysis and comparison with the series of proved cases of anterior infarction.

All records were taken on an English Cambridge electrocardiograph. Each of the four leads was standardized so that a difference in potential of 1 mv. was recorded by a deflection of 1 cm. in the finished electrocardiogram. The chest electrode consisted of a metal disk, 3 cm. in diameter, which was firmly held to the selected spot by a rubber band encircling the chest.



a. *b.* *c.* *d.* *e.* *f.* *g.*

Fig. 5.—W.D., March 20, 23, 25, and 28 and April 1 and 8, 1939, and May 21, 1940. Attacks of precordial pain, March 17 and 18, 1939, followed by fever, leucocytosis, and pericardial friction rub. Lead IVF alone shows indisputable evidence of recent anterior infarction in the first three records taken during the first week after the attacks. During the second and third weeks, the limb leads also show typical diagnostic changes. However, the sole residual evidence of the infarct fourteen months later is to be found in the absence of the R wave and the negative T wave of symmetrical limbs in Lead IVF.

Most of the records were taken by the technician who was instructed to attempt to locate the apex beat by palpation when doing Lead IVF and to place the chest electrode on the outer border of the impulse. If no apical impulse could be palpated, the electrode was to be placed in the fifth left intercostal space in the midclavicular line. Thus, in this study, Lead IVF is a combination of true Lead IVF and Lead CF_4.

Cases of cardiac infarction were arbitrarily divided into "recent" and "old" groups for the purpose of analysis of the electrocardiograms. A case was considered recent if a record was obtained within one month following the acute attack; otherwise, it was included in the old group.

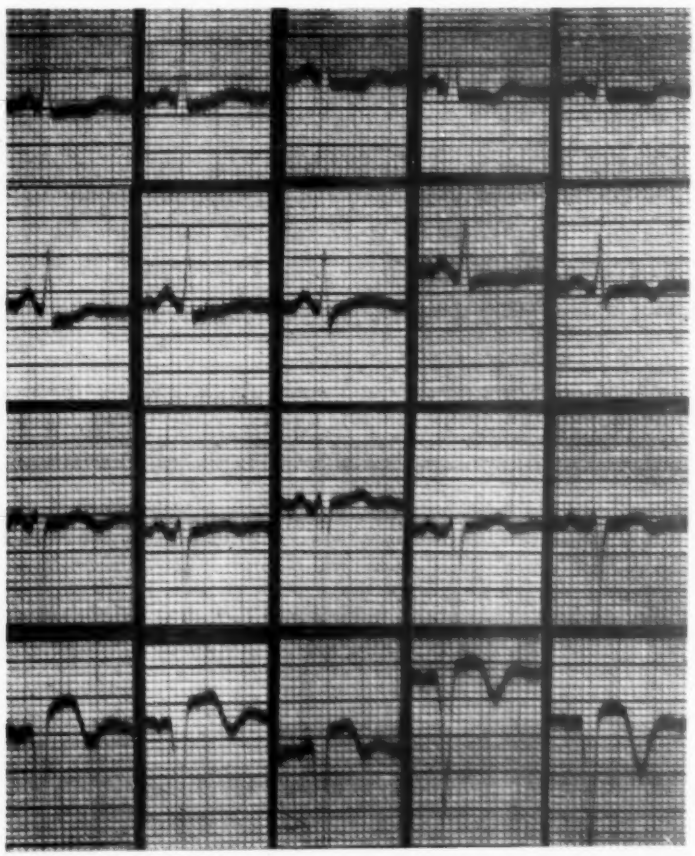
The group of recent infarctions was subdivided into four classes: (1) anterior, (2) posterior, (3) multiple or extensive, and (4) atypical. The cases of old infarction were subdivided into anterior and posterior groups for

further study. Included in the group of old anterior infarcts are many cases in the recent group recalled for further electrocardiographic study.

Recent Anterior Infarcts.—As shown in Table I, 152 cases of recent anterior infarction were analyzed and grouped into four subdivisions:

TABLE I. RELATIVE DIAGNOSTIC VALUE OF LEAD I AND LEAD IV IN 152 CASES OF "RECENT" ANTERIOR INFARCTION

DIAGNOSIS CONFIRMED BY	NUMBER OF CASES	INITIAL POSITIVE DEFLECTION, QRS,		
		ABSENT	SMALL	NORMAL
a. Lead IV only (29 cases):				
Examined post mortem	9	7	2	0
Clinical diagnosis only	20	20	0	0
b. Lead IV superior to Lead I (35 cases):				
Examined post mortem	8	5	2	1
Clinical diagnosis only	27	25	2	0
c. Leads I and IV equal (76 cases):				
Examined post mortem	15	12	2	1
Clinical diagnosis only	61	57	3	1
d. Lead I only (12 cases):				
Examined post mortem	2	0	0	2
Clinical diagnosis only	10	0	0	10
Total number of cases	152	126	11	15
Total number of cases examined post mortem	34	24	6	4



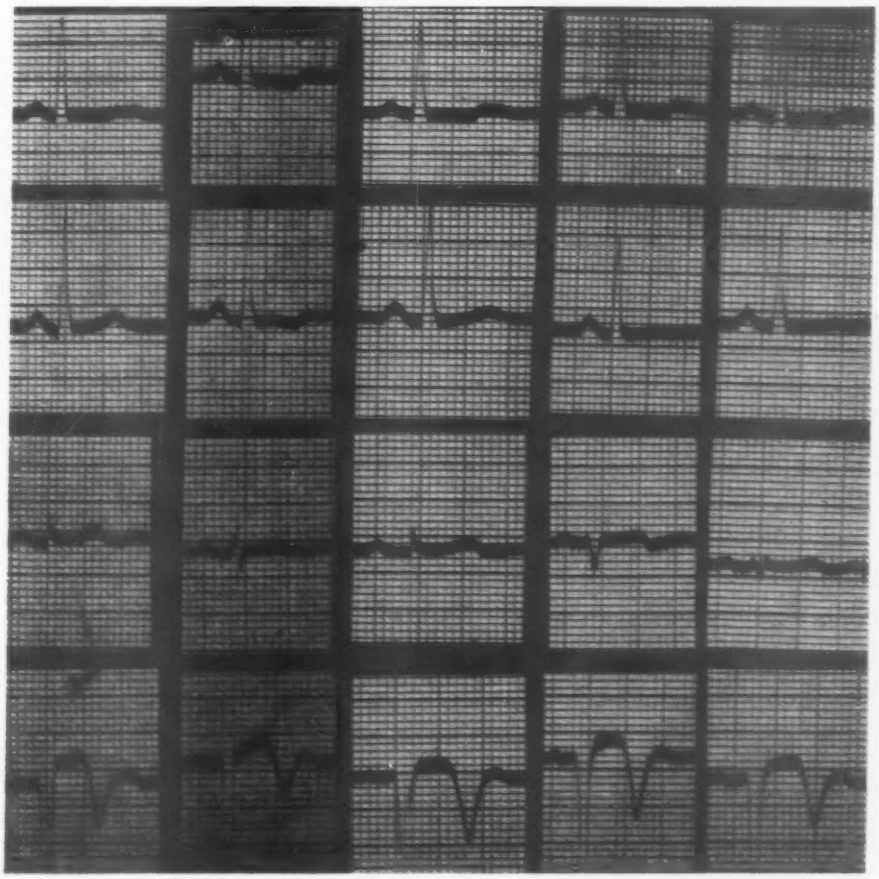
a. b. c. d. e.

Fig. 6.—E.C., Jan. 2, 5, 8, 11, and 16, 1940. Attack Jan. 1, 1940. The diagnosis of recent anterior infarction could be suspected in the limb leads from the development of negative T waves in Leads I and II. In any single record, however, the diagnosis is made with certainty in Lead IVF only. No post-mortem examination.

a. Lead IV alone showed changes diagnostic of anterior infarction in one or more records in 29 cases (19 per cent). Of 34 cases examined post mortem, nine (26 per cent) showed definite diagnostic changes in Lead IV only. Further study of these cases is recorded in Table II.

TABLE II. ANTERIOR INFARCTION: CHARACTERISTIC CHANGES IN LEAD IV ONLY

DIAGNOSTIC CHANGES EVIDENT	NUMBER OF CASES	NUMBER CONFIRMED BY POST-MORTEM EXAMINATION
In only record made (Fig. 2)	4	1
In only 1 record of a series (Figs. 3 and 4)	7	2
In more than 1 record (usually initial 2 or 3 of a series of 6 or 8 records) (Fig. 5)	8	0
In all records of a series (Figs. 6 and 7)	10	6
Total	29	9



a. b. c. d. e.

Fig. 7.—E.R., Aug. 22, 27, and 30, and Sept. 6 and 16, 1938. Attacks one year and two weeks prior to initial record. In spite of the marked change in T waves in the standard leads, Lead IVF alone contains certain evidence of anterior infarction.

b. The chest lead showed much more obvious and determinate evidence of recent anterior infarction than the minimal diagnostic changes in the limb leads in 35 (23 per cent) of the 152 cases. In the cases examined post mortem, eight (24 per cent) of the 34 cases fell into this group.

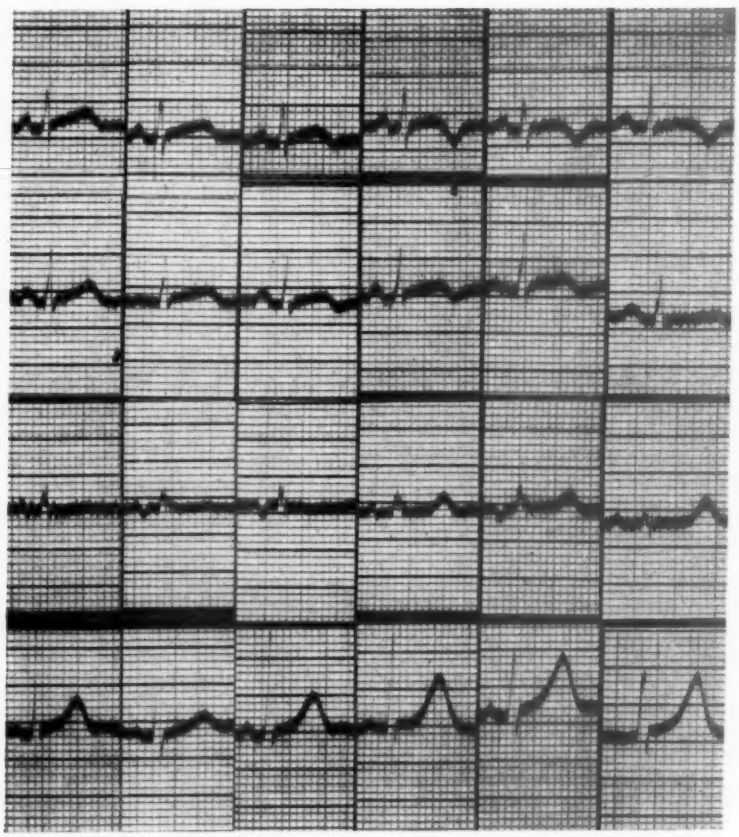
c. All four leads showed equally and simultaneously the changes of recent anterior infarction in 76 cases (50 per cent). Fifteen of these (44 per cent of the 34 cases examined post mortem) were proved anatomically.

d. In 12 cases (8 per cent) with diagnostic changes in the limb leads, Lead IV showed minimal, if any, changes (Table III). Two of these (6 per cent of the 34 cases examined post mortem) came to autopsy.

Since changes in the QRS complex in recent anterior infarction are more reliable diagnostically than T-wave changes alone, the initial deflection of the QRS complex has been examined in each case of recent anterior infarction (Table I). One hundred twenty-six cases (83 per cent) showed a negative

TABLE III. ANTERIOR INFARCTION: MINIMAL OR NO CHANGE IN LEAD IV

1. No change in Lead IV (Fig. 8)		4
2. T_4 changes only—QRS not altered		8
a. T_4 transiently low and notched (Fig. 9)	1	
b. T_4 slightly negative or diphasic	2	
c. T_4 deeply negative (Fig. 10)	5	
Total number of cases		12



a. *b.* *c.* *d.* *e.* *f.*

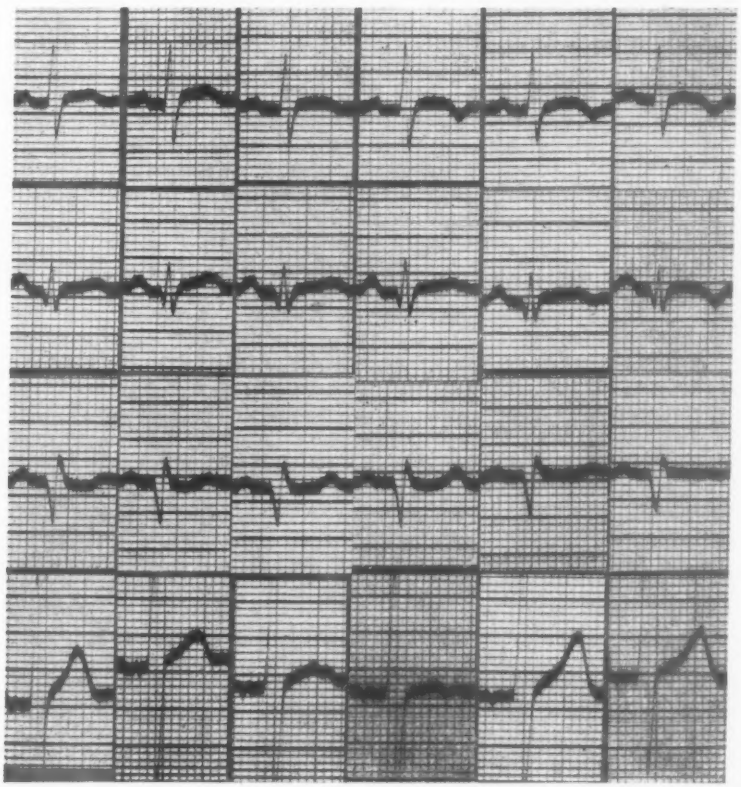
Fig. 8.—F.R., Jan. 20, 21, 23, 27, and 28, and Feb. 6, 1941. Attacks Jan. 14 and 16, 1941. While the limb leads were slow to change, the diagnosis of recent anterior infarction could not be made in Lead IVF which remained normal throughout the period of observation.

initial deflection; 11 cases (7 per cent) showed a positive initial deflection under 2 mm., i.e., a small R_4; the remaining 15 cases (10 per cent) showed a positive initial deflection greater than 2 millimeters.

Of the 34 cases which came to autopsy, 24 (70 per cent) showed an initial negative deflection of QRS_4; six cases (18 per cent) showed a small initial R_4; and four cases (12 per cent) had an initial R_4 greater than 2 mm. in height.

The majority of cases of recent anterior infarction presented an initial negative deflection of QRS_4, with or without the disappearance of R_4, in the first record which in many cases was made within a few hours of the attack.

Old Anterior Infarcts.—The results of analysis of 97 cases of "old" anterior infarction are found in Table IV. In 57 cases no record was obtained during the month after the acute attack. Fifteen of these were confirmed at autopsy. The remaining 40 of the 97 cases are tabulated as "follow-up" records; they represent cases included previously in the group of "recent" anterior infarcts, in which at least one record was obtained several months after the initial series.



a. *b.* *c.* *d.* *e.* *f.*

Fig. 9.—S.G., June 26, 27, 28, and 29, and July 3 and 14, 1939. Attack June 24, 1939. Diagnosis of recent anterior infarction can be made in the limb leads in the initial record, while Lead IVF is normal. While the T wave in Lead IVF becomes transiently low and notched in serial records, the diagnosis of anterior infarction is at no time possible from Lead IVF alone: R_4 remains normal in height throughout the series.

Lead IV showed the sole diagnostic evidence of anterior infarction in 46 cases (48 per cent) and much better and more certain evidence than Lead I in eight (8 per cent). The evidence was equally good in Leads I and IV in 36 cases (37 per cent). Lead I showed the only evidence in one case (1 per cent). In addition, there were six cases in the "follow-up" group which showed no residual electrocardiographic sign of the former attack.

An initial negative deflection of QRS_4 was found in 74 (76 per cent) of the 97 cases. An initial positive deflection under 2 mm. was present in 15 cases (16 per cent); while R_4 was over 2 mm. in eight cases (8 per cent).

It is interesting to scrutinize more closely the records of the follow-up group of 40 cases (Table V). These later records were all taken from six

TABLE IV. RELATIVE DIAGNOSTIC VALUE OF LEAD I AND LEAD IV IN NINETY-SEVEN CASES OF "OLD" ANTERIOR INFARCTION

DIAGNOSIS CONFIRMED BY	NUMBER OF CASES	INITIAL POSITIVE DEFLECTION, QRS_4		
		ABSENT	SMALL	NORMAL
Lead IV only:				
Clinical diagnosis only	16	16	0	0
Examined post mortem	6	3	3	0
Follow-up	24	22	2	0
Total	46	41	5	0
Lead IV superior to Lead I:				
Clinical diagnosis only	7	7	0	0
Examined post mortem	1	0	1	0
Follow up	0	0	0	0
Total	8	7	1	0
Leads I and IV equal:				
Clinical diagnosis only	18	12	6	0
Examined post mortem	8	4	3	1
Follow-up	10	10	0	0
Total	36	26	9	1
Lead I only:				
Clinical diagnosis only	1	0	0	1
Examined post mortem	0	0	0	0
Follow-up	0	0	0	0
Total	1	0	0	1
Summary:	6	0	0	6
No remaining evidence (follow-up)				
Clinical diagnosis only	42	35	6	1
Examined post mortem	15	7	7	1
Follow-up	40	32	2	6
Total	97	74	15	8

months to two years after the patient was admitted to the hospital with the acute attack. In 24 cases Lead IV alone showed remaining evidence of the former anterior infarction; an initial negative deflection of QRS_4 only in 13 cases; an initial negative deflection of QRS_4 and a negative T_4 in nine cases; and a small initial positive deflection of QRS_4 in the remaining two cases, one of which also showed a negative T_4.

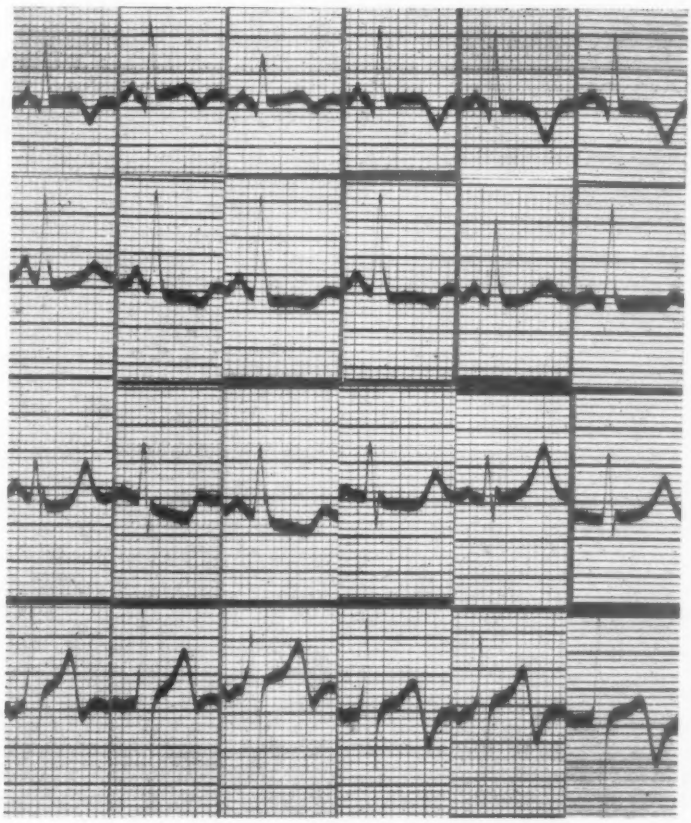
Leads I and IV were considered equally diagnostic of old anterior infarction in ten of these 40 cases. In eight of the ten, T_1 and T_4 were negative and coronary in shape, and were associated with an initial negative deflection in QRS_4. In the other two cases, T_4 had returned to a positive deflection.

TABLE V. "OLD" ANTERIOR INFARCTION: FOLLOW-UP RECORDS ON FORTY CASES

REMAINING DIAGNOSTIC EVIDENCE IN		NUMBER OF CASES
Lead IV only:		
Initial negative deflection of QRS_4 only		13
Initial negative deflection of QRS_4 and negative T_4		9
R_4 under 2 mm. only		1
R_4 under 2 mm. and negative T_4		1
		24
Leads I and IV equally:		
Initial negative deflection of QRS_4		10
(T_1 negative: T_4 positive	2 cases	
T_1 and T_4 negative	8 cases)	
No residual evidence of former attack		6
Summary:		
T_1 remained negative in 10 cases (25 per cent)		
T_4 remained negative in 18 cases (45 per cent)		
QRS_4 continued to show evidence of former attack in 34 cases (85 per cent)		

In the remaining six cases, complete reversion to normal had taken place.

Posterior Wall Infarction.—In recent posterior infarction the typical finding in Leads I and IV is temporary depression of the RT segments. A return to former levels is usually seen in the course of one to two weeks. In 57 (70 per cent) of a total of 82 cases, Leads I and IV showed these changes equally. Lead IVF was either the only lead to show RT depression or showed it much more obviously in 20 cases (24 per cent). Lead I alone showed this change in five cases (6 per cent).



a. *b.* *c.* *d.* *e.* *f.*

Fig. 10.—J.S., Aug. 13, 16, 19, and 22, and Sept. 9 and 16, 1941. Angina pectoris for three months. Prolonged pain Aug. 9, 1941. The diagnosis of anterior infarction is obvious in the limb leads. T wave in Lead IVF becomes progressively more negative; the R wave remains at normal height.

Neither Lead I nor IV showed any change which contributed to the diagnosis in old posterior wall infarction. There were 35 such cases.

Seven cases of recent posterior infarction and three cases of old posterior infarction came to autopsy. The electrocardiograms from these cases had shown R_4 normal in height in seven and under 2 mm. in the other three cases; in none was it absent nor was there an initial negative deflection.

Multiple and Extensive Infarction.—Under this heading are considered those cases which in serial records do not fall readily into either the T_1:T_4 type (anterior) or the T_3 type (posterior). This group is composed of 47 cases which have been divided into three arbitrary groups.

1. Cases showing negative T waves in all four leads: There were 24 cases in this subdivision. Six came to autopsy (Table VI). In four of the six cases

TABLE VI. ELECTROCARDIOGRAPHIC CHANGES IN CASES OF MULTIPLE AND EXTENSIVE INFARCTION IN WHICH DIAGNOSIS WAS CONFIRMED AT AUTOPSY

	NO.
1. $T_{1, 2, 3, \text{ and } 4}$ negative (6 cases):	
a. Infarction of anterior and posterior walls through septum: single attack, 1; multiple attacks, 3 (R_4 absent in 2 cases; R_4 small in 2 cases)	4
b. Infarction of anterior, lateral, and posterior walls (one attack, with R_4 absent, in both cases)	2
2. Lead IV behaved in manner opposite to that of limb leads (3 cases):	
a. Limb leads indicative of posterior infarction: Lead IV indicative of anterior infarction	2
i. Recent infarction of anterior and posterior walls of left ventricle and the adjacent anterior portion of septum—1 case	
ii. Old anterior and posterior infarcts plus small multiple pulmonary infarcts—1 case ($T_{2, 3, 4}$ negative; $Q_{2, 3, 4}$)	
b. Limb leads indicative of anterior infarction: Lead IV indicative of posterior infarction. Old and recent infarcts of anterior and posterior walls of the left ventricle and septum (R_4 normal)	1
3. Multiple infarction (1 case): Two infarcts—1 lateral and 1 posterior	1

examined post mortem, the infarct extended through the septum to involve both the anterior and posterior walls of the left ventricle. In the remaining two cases, the large infarct extended laterally around the left ventricle to lie both anteriorly and posteriorly. Ten of the 24 patients in this group suffered a single attack; 14 had more than one attack. The initial deflection of QRS_4 was negative in 15 of the 24 cases; positive but small in three; and normal in height in six cases.

2. Cases in which Lead IV behaved in the opposite manner to changes in the limb leads: Twelve cases fell into this group. In eight of these Lead IV showed changes either typical or very suggestive of anterior infarction, while limb lead changes alone indicated posterior wall localization. In the other four cases the reverse was true: limb leads suggested anterior infarction, while Lead IV indicated posterior wall involvement.

Three of the 12 cases came to autopsy. One, in which Lead IV suggested anterior infarction while the limb leads suggested posterior infarction, showed recent infarction of anterior and posterior portions of the left ventricle and of the anterior (adjacent) portion of the interventricular septum. In another case with the same electrocardiographic findings, old anterior and posterior cardiac infarcts were demonstrated along with small multiple pulmonary infarcts. The electrocardiographic findings of negative T waves in Leads II, III, and IV, together with $Q_{2, 3, 4}$, are thus accounted for. The remaining case in which the limb leads, in a single record taken just before death, suggested anterior infarction and Lead IV posterior infarction, showed old and recent infarcts of the anterior and posterior walls of the left ventricle and septum.

3. Cases of multiple infarction under clinical observation throughout the course of more than one attack of cardiac infarction: In each of the 11 cases in this group electrocardiographic changes gave adequate evidence of two or more separate clinical episodes diagnosed cardiac infarction. It is interesting to note that in two of five cases with evidence of an older anterior infarct upon which had been superimposed a recent posterior infarct the well-marked initial negative deflection of QRS_4, that developed as the result of the anterior infarction, completely disappeared leaving a normal R_4 (initial positive deflection) with the advent of the posterior infarct.

Atypical Infarcts.—There were 15 cases with history suggestive of recent coronary occlusion in which there was evidence of cardiac infarction, such as transient fever and leucocytosis, but in which serial electrocardiographic records failed to show diagnostic changes. None of these cases came to autopsy.

Coronary Occlusion Without Infarction.—In 18 cases in which the history suggested recent coronary occlusion, the clinical course was not characterized by fever and leucocytosis. Electrocardiograms in these cases commonly showed T-wave changes, usually without changes in the QRS. These could not be considered cases of cardiac infarction. In the majority, T_4 became transiently negative. Three of the 18 cases in this group came to autopsy. It is of interest that one case with recent thrombosis of the anterior descending branch of the left coronary artery without visible infarction in the ventricle had shown a definite initial negative deflection of QRS_4 (Q_4).

SPECIAL STUDY OF 165 CASES EXAMINED POST MORTEM

In order to visualize more clearly the significance of the change which usually occurs in the QRS complex of Lead IVF with the advent of anterior infarction, 165 cases examined post mortem were selected for special study. Of these, 58 cases showed anterior wall infarction, and 107 showed other forms of heart disease. A striking contrast is thus presented by these two groups with respect to the initial deflection of the QRS complex (Table VII).

TABLE VII. ELECTROCARDIOGRAPHIC FINDINGS IN FIFTY-EIGHT CASES OF ANTERIOR INFARCTION AND 107 CASES OF OTHER FORMS OF HEART DISEASE EXAMINED POST MORTEM

CLINICAL DIAGNOSIS	NUMBER OF CASES	INITIAL POSITIVE DEFLECTION, QRS_4		
		ABSENT	SMALL	NORMAL
Anterior infarcts (in four-year period):				
Recent	35	25	6	4
Old	14	6	7	1
Complicated	9	6	1	2
Total	58 (100%)	37 (64%)	14 (24%)	7 (12%)
Infarction other than anterior (in four-year period)	11	0	4	7
Coronary occlusion without infarction (in four-year period)	3	1	0	2
Other forms of heart disease (in thirty-month period)	93	6	19	68
Total	107 (100%)	7 (6.5%)	23 (21.5%)	77 (72%)

The chief cardiac changes of significance, in relation to QRS_4, found at autopsy in the 165 cases selected for special investigation were as follows:

$Q_4\ R_4$ (nine cases):
- Anterior infarcts were found in — 7 cases
- Recent thrombosis of the anterior descending branch of the left coronary artery was found in — 1 case
- Pulmonary embolism but no cardiac infarction was found in (Q_4 was present in only one of four serial records on this case) — 1 case

R_4 absent (35 cases):
- Anterior infarction was found in — 30 cases
- Pulmonary embolism was found in — 3 cases
- Pericarditis was found in — 1 case
- Aortic valvular disease with left ventricular hypertrophy was found in — 1 case

R_4 small (2 mm. or less) (37 cases):

Anterior infarction (left bundle branch block in 2 cases) was found in	14 cases
Left ventricular hypertrophy curve (result of hypertensive cardiovascular disease or aortic valvular disease) was found in	12 cases
Lateral wall infarction was found in	4 cases
Posterior infarction together with coronary sinus thrombosis was found in	1 case
Syphilitic aortitis with posterior infarction was found in	1 case
Periarteritis nodosa of coronary arteries was found in	1 case
Pulmonary heart disease was found in	1 case
Miscellaneous lesions (left bundle branch block in 1 case) were found in	3 cases

R_4 normal height (over 2 mm.) (84 cases):

Anterior infarction (in 2 cases, Lead IV suggested posterior infarction) was found in	7 cases
Posterior infarction was found in	8 cases
Recent coronary thrombosis without infarction was found in	2 cases
Left ventricular hypertrophy curve was found in	28 cases
Miscellaneous forms of heart disease other than above were found in	39 cases

Other investigators[12, 16, 18, 21, 22, 23] have pointed out that changes in QRS_4 are more reliable diagnostic evidence of anterior infarction than T_4 changes alone. This observation has been confirmed in this series of cases by a negative T_4 associated with the following conditions: (1) left ventricular hypertrophy, a result of hypertensive cardiovascular disease or aortic valvular disease; (2) pulmonary embolism; (3) pericarditis; (4) a few cases of arteriosclerotic heart disease without infarction and without a left ventricular hypertrophy curve; (5) certain adults apparently without heart disease, including some adolescents in whom the clinical diagnosis was "neurasthenia"[24]; (6) following an arrhythmia such as paroxysmal auricular tachycardia, paroxysmal flutter or fibrillation (transiently negative T_4 in serial records); (7) nephritis, acute and chronic; (8) myxedema; (9) Addison's disease; (10) congenital heart disease; and (11) digitalis effect. There are no records on children in this series.

DISCUSSION

With such a large variety of conditions giving rise to a negative T wave in Lead IVF, it is fortunate that with the advent of anterior infarction changes occur as described above, e.g., the appearance of an initial negative deflection of the QRS (Q wave) with coincident reduction or absence of the positive deflection (R wave). The significance of the presence of a Q wave in Lead IVF has received extensive study. Master and associates[21] found that 88 per cent of 120 cases exhibiting a Q_4 were probably anterior infarcts. Vander Veer and Edwards[22] report that 67 per cent of 102 cases of absent R_4 had anterior infarction. Cutts, Clagett, and Fulton,[23] in a group of 30 cases with similar electrocardiographic findings which were examined post mortem, found evidence of anterior infarction in 87 per cent.

In Table VII it is shown that, of the 58 cases of anterior infarction examined post mortem in the present series, 64 per cent showed an initial negative deflection, which is in sharp contrast to 6.5 per cent of 107 cases of other forms of heart disease. Conversely, an initial positive deflection (R) in excess of 2 mm. was found in 72 per cent of other forms of heart disease, while only 12 per cent of anterior infarction cases presented a normal R_4.

Since the series of cases of infarction extended over a longer period (48 months) than the series of other forms of heart disease (thirty months), consideration of the 44 cases presenting an initial negative deflection of QRS_4 could not be reduced to percentage of those showing anterior infarction without weighting the figures. With proper weighting, 77 per cent of cases with an initial negative deflection showed anterior infarction; of the cases with a normal positive initial deflection, 5.6 per cent had anterior infarction.

Difficulty may be encountered in the correct interpretation of an initial positive deflection (R_4) less than 2 mm. in height. Levine and Levine[25] state that 50 per cent of cases of angina pectoris showing small initial positive deflection of QRS_4 have had anterior infarction. After weighting, 29 per cent of all cases in this series with an initial positive deflection less than 2 mm. in height showed anterior infarction at post-mortem examination.

Value of Lead IV in Anterior Infarction.—Recent infarction: As noted above, 29 (19 per cent) of 152 cases of anterior infarction showed diagnostic changes in Lead IVF alone in at least one record of a series done on an individual case. These may be subdivided as follows:

1. In 14 cases (9 per cent) diagnostic changes were entirely lacking in the limb leads: in serial records on ten cases (6 per cent); and in the only record obtained on four cases (3 per cent). The usual cause of failure of the limb leads to show certain evidence of anterior infarction was pre-existing electrocardiographic abnormality, such as a left ventricular hypertrophy curve.

2. In 15 cases (10 per cent) the electrocardiographic diagnosis was established by Lead IVF hours or days in advance of the appearance of diagnostic changes in the limb leads.

In addition, there were 35 cases (23 per cent) of recent anterior infarction in which the chest lead showed much more obvious and definite diagnostic changes than the minimal changes in the limb leads. Thus in 42 per cent of 152 cases Lead IVF was either of considerable or of paramount importance to the electrocardiographic diagnosis.

When the series of 34 cases examined post mortem is segregated, Lead IVF is seen to have an even greater value. In 26 per cent of these cases Lead IV alone revealed the diagnosis, while it had a marked advantage over the limb leads in contributing to the correct diagnosis in a further 24 per cent. Thus, in half the proved cases of anterior infarction Lead IVF provided more definite diagnostic evidence than the limb leads.

These findings are in agreement with those of other investigators. Goldbloom[4] found that Lead IV alone showed diagnostic changes in 7.5 per cent of cases of coronary occlusion. Bohning and Katz[26] state that, as a rule, infarction is more easily diagnosed early from Lead IV. Willcox and Lovibond[27] found that 35 per cent of 20 cases showed the only significant electrocardiographic changes in Lead IV soon after the attack, while the same was true in 20 per cent of their series of 20 cases in which the infarcts were slightly older. Lieberson and Goldbloom[28] summarized their report of seven years' experience with chest leads by stating that Lead IV "increases the efficiency of the conventional leads in detecting and corroborating evidence of acute coronary thrombosis in about 10 per cent of the cases if serial (and occasionally multiple) precordial leads are used; by about 4 or 5 per cent when single four-lead electrocardiograms are used."

Old infarction: Lead IV had a still greater advantage over the limb leads in the diagnosis of old anterior infarction.[2, 28, 29] Lead IV provided the sole diagnostic evidence in 46 (48 per cent) of the 97 cases, while in a further 8 per cent the evidence was much better in Lead IV than in the limb leads.

Attention has been directed to the persistence of the altered QRS_4 as the result of anterior infarction.[12, 16, 21, 22] In the present series of cases, the frequency with which QRS_4 alone showed remaining diagnostic evidence of the former attack has been noted, T_4 having reverted to an upright deflection in the majority of cases.

Atypical infarction: Following acute occlusion of a large branch of one of the coronary arteries, the size and extent of infarction of the myocardium depend largely on the degree of atherosclerotic narrowing present in the remainder of the branches of the coronary tree. Thus, it is not surprising that the electrocardiographic tracing frequently does not conform to the typical anterior or posterior pattern. As noted in the review of cases of atypical infarction, Lead IVF may definitely increase the value of the electrocardiogram in localizing the infarct by behaving in a manner opposite to that of the limb leads.

SUMMARY AND CONCLUSIONS

1. Analysis of the electrocardiographic records of cases of cardiac infarction admitted to the public ward of the Toronto General Hospital during a four-year period has been made. The records consist of the standard limb leads and Lead IVF.

2. Study was also made of the electrocardiographic records of all cases showing abnormality in the ventricular complex (QRS-T) admitted during the first thirty months of the same four-year period. However, only the records of those cases coming to autopsy were analyzed for comparison with the proved cases of cardiac infarction.

3. Lead IVF was found to present the sole diagnostic evidence of recent anterior infarction in 19 per cent of 152 cases, and in 48 per cent of 97 cases of old anterior infarction.

4. Lead IVF presented the main diagnostic evidence in a further 23 per cent of cases of recent anterior infarction, and in a further 8 per cent of old anterior infarction.

5. Thus, Lead IVF had a definite advantage over the limb leads in contributing to the electrocardiographic diagnosis in 42 per cent of recent and in 56 per cent of old anterior infarction cases.

6. In 47 cases of infarction showing changes other than the typical anterior or posterior distribution, Lead IVF was important to the electrocardiographic localization of the infarct by behaving in a manner opposite to the changes in the limb leads in 12 cases (25 per cent).

7. Changes in QRS_{4F} in anterior infarction were described in detail and their outstanding characteristics compared with the QRS_4 findings in anatomically proved cases of other forms of heart disease, including infarction other than anterior.

8. The conditions other than anterior infarction associated with inversion of T_4 have been enumerated. The electrocardiographic diagnosis of anterior infarction was much more reliable when the ventricular complex as a whole in Lead IVF underwent characteristic changes.

9. Of the cases examined post mortem, in which an initial negative QRS_4 deflection had been recorded, 77 per cent showed anterior infarction.

10. Approximately 29 per cent of cases examined post mortem, which had presented an initial positive deflection less than 2 mm. in height, showed anterior infarction.

11. Of the cases with a normal initial positive QRS_4 deflection which came to autopsy, 5.6 per cent showed anterior infarction.

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OBSERVATIONS ON TWO PATIENTS WITH PAROXYSMAL VENTRICULAR TACHYCARDIA TREATED BY THE INTRAVENOUS ADMINISTRATION OF QUINIDINE LACTATE

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PAROXYSMAL ventricular tachycardia[1] is generally, but not always, associated with grave heart disease. In most instances it is associated with disease of the coronary arteries, occurring in 5 per cent of all myocardial infarctions. Ventricular tachycardia is not always fatal when it occurs with coronary occlusion. It may be transient lasting for only a few hours and causing no particular problem in treatment; on the other hand, it may be persistent and resistant to therapy and may terminate fatally. It has occasionally been witnessed following the administration of digitalis[2] and has also been precipitated by slight physical exertion[3] in individuals without other clinical evidence of heart disease. Experimentally it has occurred in cats following the administration of low tension chloroform vapor,[4] and Robinson and Herrmann[5] found it frequently in dogs following ligation of the coronary arteries. The purpose of this paper is to present some of the aspects in diagnosis and treatment of ventricular tachycardia, including the report of two unusual cases treated by the intravenous administration of quinidine lactate.

CASE REPORTS

CASE 1.—W. C. This patient was admitted to the University Hospitals on Oct. 14, 1942. Two days previously, he had experienced a typical attack of coronary occlusion with precordial pain radiating to both shoulders and up the back of his neck. The sharp pain had been replaced by a dull precordial distress and was accompanied by nausea and vomiting.

Physical examination on admission, revealed a rather obese 52-year-old, acutely ill, orthopneic, disoriented, cyanotic white man with a flushed facies. The pupils were contracted (due to the administration of morphine), and the tongue was dry. The left border of the heart was 2 cm. to the left of the midclavicular line. The heart tones were distant and a variable friction rub was present all over the precordium. The heart rate was approximately 200 beats per minute, but the rhythm was regular. The systolic arterial pressure was 90 and the diastolic was 80 mm. of mercury. The lungs contained a few moist râles at the bases. No other significant physical findings were present.

An electrocardiographic tracing was taken immediately after admission, which revealed ventricular tachycardia at a rate of 210 beats per minute (Fig. 1). At 7:45 P.M., approximately thirty minutes after admission, quinidine lactate, in a dosage of 0.65 Gm., was administered intravenously. An electrocardiographic tracing taken seven minutes later revealed a normal mechanism with a rate of 90 beats per minute. The patient then received, orally, 0.2 Gm. (3 grains) of quinidine sulfate, 30 mg. (½ grain) of papaverine hydrochloride, and 0.2 Gm. (3 grains) of theophylline ethylenediamine four times daily, and, in addition intranasal oxygen.

During his hospital stay, from Oct. 14, 1942, to June 12, 1943, the patient had six more attacks of ventricular tachycardia, all proved by electrocardiographic tracings. Each attack was successfully stopped by the intravenous administration of quinidine lactate in doses varying from 0.325 Gm. to 1.3 Gm. During the fifth attack, during which 0.65 Gm. of quini-

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dine lactate was injected intravenously without effect, and 0.26 Gm. was repeated thirty minutes later, the patient's heart tones suddenly stopped, he had a generalized convulsion, and approximately three to five seconds later he vomited, his heart tones became audible, and the cardiac mechanism had returned to normal. During the first five months of hospitalization, he received quinidine sulfate orally in doses varying from a minimum of 3 grains four times per day to 5 grains six times per day. He was maintained, during the last three months of his hospital stay, without recurrence of his attacks on a total oral dose of 30 grains of quinidine sulfate per day.

Following discharge from the hospital, he took quinidine rather spasmodically and finally discontinued it. On July 17, 1943, he apparently had another episode of coronary occlusion with severe precordial pain radiating into both arms. After this the symptoms recurred similar to those previously experienced during the attacks of tachycardia.

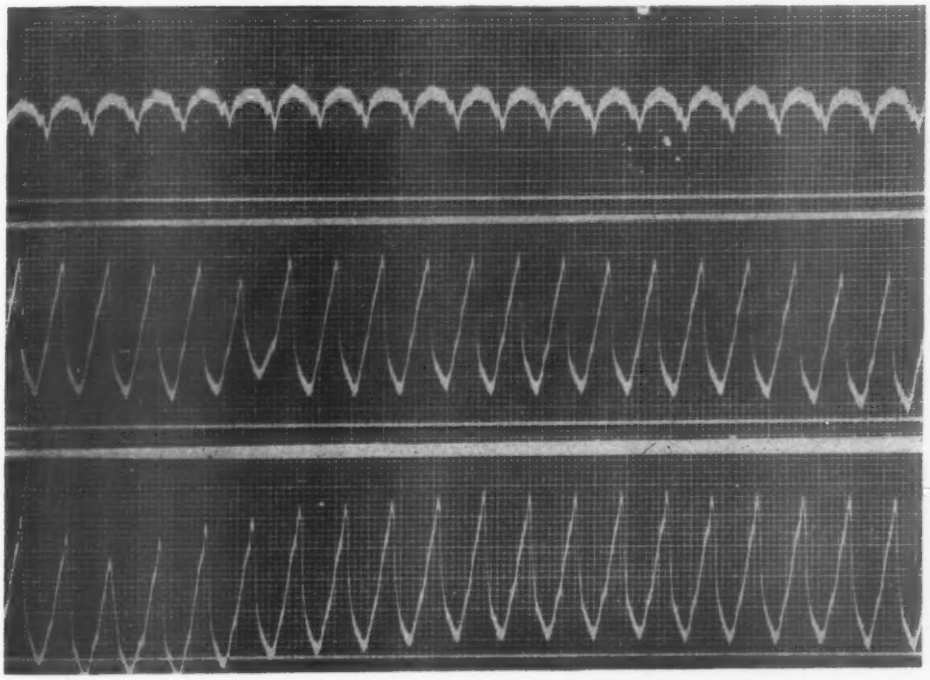

Fig. 1.—Electrocardiographic tracing of paroxysmal ventricular tachycardia.

He returned to the hospital on Oct. 10, 1943, for five weeks during which time he was maintained on a dose of 30 grains of quinidine sulfate orally without recurrence of the tachycardia. An electrocardiographic tracing (Fig. 2), obtained on this admission, revealed evidence of a fairly recent anterior coronary infarction. On Nov. 19, 1943, he was again admitted during an attack of ventricular tachycardia which was successfully converted to a normal mechanism by the intravenous administration of quinidine lactate in divided doses of 0.65 Gm. each. He remained in the hospital three months during this visit and received 30 grains of quinidine sulfate orally daily without further attacks.

The patient has continued to take quinidine sulfate faithfully and when last seen, May 25, 1944, he had had no further attacks of tachycardia. An electrocardiographic tracing taken at that time was essentially normal except for an occasional premature ventricular contraction.

CASE 2.—B. H. This patient was admitted to the University Hospitals on Feb. 16, 1944. In the summer of 1937, this 47-year-old white man, while lifting a barrel, suddenly experienced a severe, vicelike pain in the substernal region. He fell to the ground but did not lose consciousness. Soon afterwards the pain disappeared and he felt all right. In the summer of 1938, he again suddenly fell to the ground without previous pain or other warning. He was not unconscious nor did he lose control of his bowel or bladder. There was no precordial distress connected with this episode. The patient was put to bed for two weeks and was given twenty drops of digitalis daily, which was soon discontinued. During the five years preceding his first admission to the University Hospitals, he had had repeated "heart attacks." These

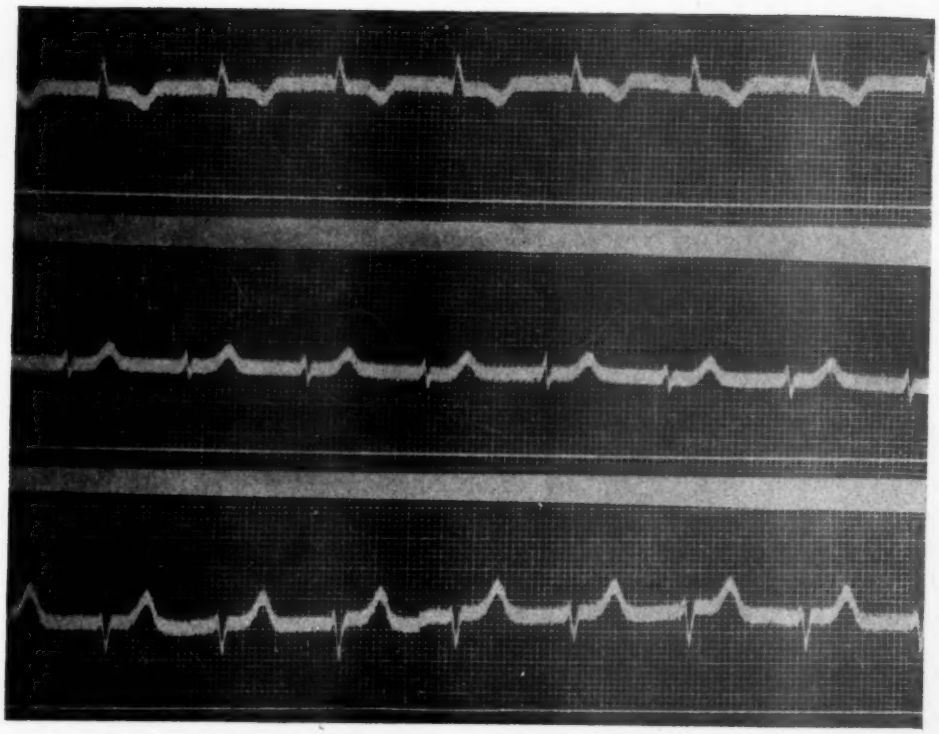

Fig. 2.—Electrocardiographic tracing of nodal rhythm in evidence of a fairly recent anterior myocardial infarction.

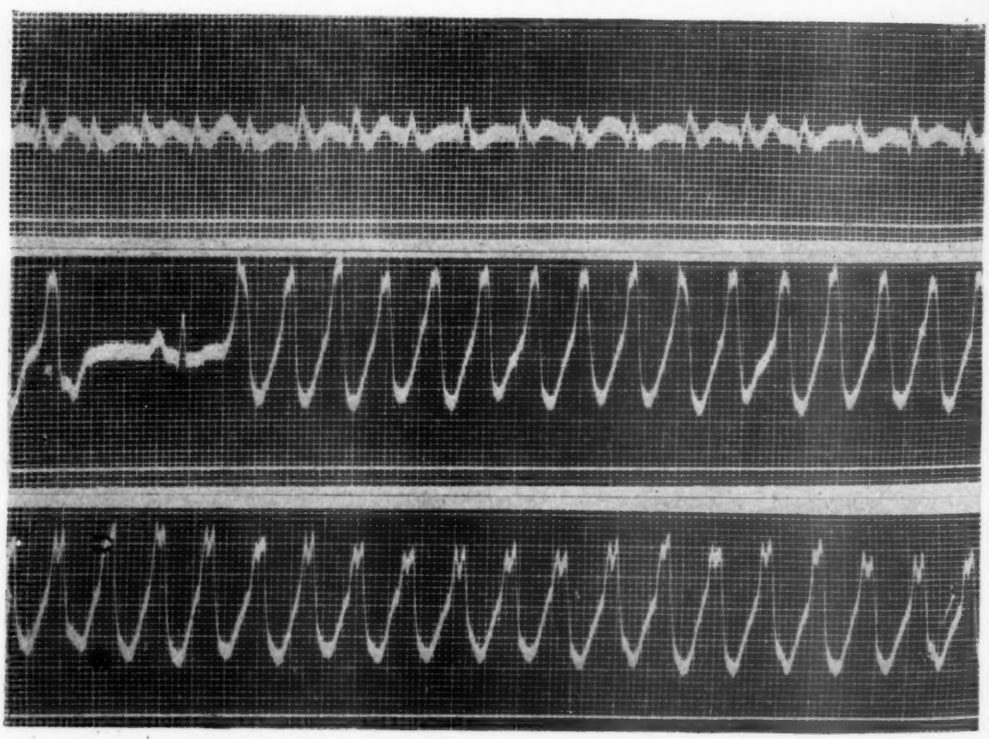

Fig. 3.—Electrocardiographic tracing of paroxysmal ventricular tachycardia with one cycle of normal mechanism in Lead II.

attacks were usually rather sudden in their onset with a rapid, "fluttery" feeling in the heart. Accompanying these attacks, there would be rather severe substernal pain which would radiate to the right shoulder and down the inner aspect of the right arm as far as the wrist. The attacks usually terminated quite suddenly, although sometimes the offset was gradual. The physician who originally saw this patient gave him quinidine sulfate in doses up to 27 grains daily, without effect, so that the medication was discontinued. The final month before his hospital admission, he had experienced considerable exertional shortness of breath, but no orthopnea, dyspnea, or ankle edema.

Physical examination revealed a moderately obese, ambulatory, 47-year-old white man without cyanosis or ankle edema. The heart was not enlarged, the rhythm was regular, and the rate was 76 beats per minute. The heart tones had a somewhat mushy quality but no definite murmurs were present. The systolic arterial pressure was 140 and the diastolic was 95 mm. of mercury. Dullness was elicited in the left lung base with some diminution in the breath sounds. No other significant physical findings were observed.

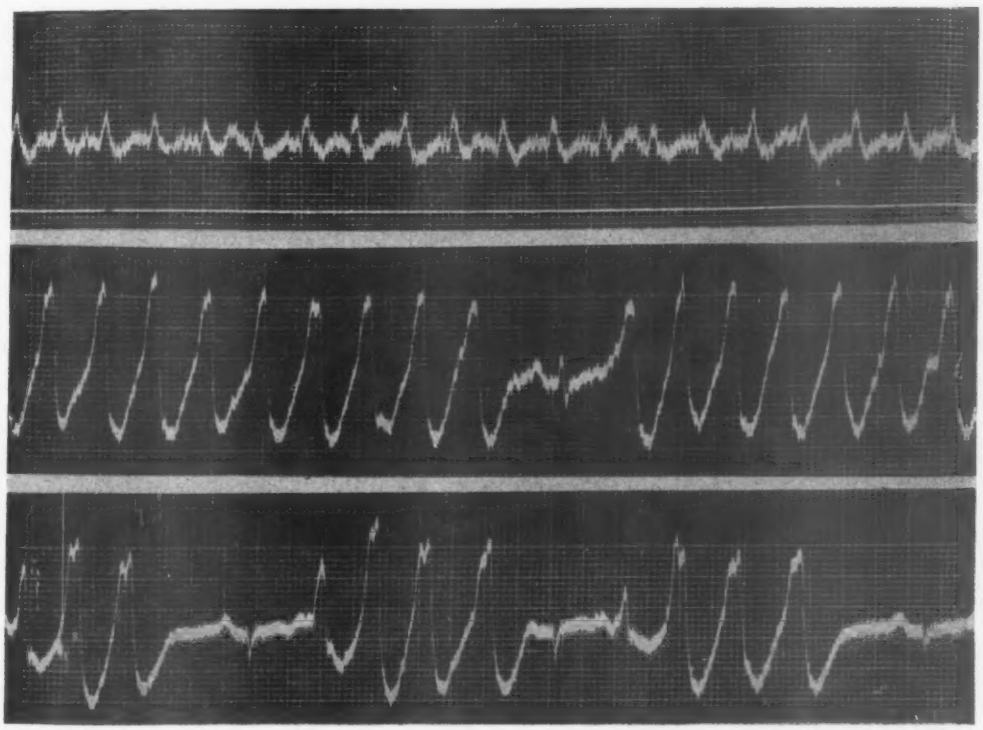

Fig. 4.—Electrocardiographic tracing of paroxysmal ventricular tachycardia with cycles of normal mechanism appearing in Leads II and III five minutes after the intravenous administration of 0.65 Gm. of quinidine lactate.

A teleroentgenogram revealed a thickening of the pleura at the left base of the lungs without cardiac enlargement. An electrocardiographic tracing taken on Feb. 16, 1944, was normal. Urinalyses and blood examinations were negative. Blood Kolmer and Kline tests were negative.

Attempts to reproduce an attack by exercise were unsuccessful. That same evening, however, the patient spontaneously developed a tachycardia with flushing of his face, mild apprehension, and rather profuse diaphoresis, but no precordial distress. An electrocardiographic tracing obtained at that time revealed ventricular tachycardia (Fig. 3). Carotid pressure failed to alter the tachycardia, and quinidine lactate in 0.65-Gm. doses administered intravenously also failed to convert it to a normal mechanism. An electrocardiographic tracing taken five minutes later (Fig. 4) showed slight alteration from the previous one. Fifteen minutes later an electrocardiographic tracing revealed the presence of auricular tachycardia with several premature ventricular beats (Fig. 5).

The patient was then placed on 3.6 Gm. (54 grains) of quinidine sulfate orally daily in divided doses. Despite its constant administration, he continued to have attacks of tachycardia, and on all subsequent electrocardiographic tracings, five in all, the attacks were ventricular in origin. The attacks lasted from twenty minutes to forty-eight hours regardless of whether or not he was receiving quinidine. Unfortunately, it was necessary for the patient to go home due to outside circumstances. Quinidine therapy was discontinued, and he was discharged on March 10, 1944, with instructions to return in one month.

While at home, he stated he had had an attack lasting from March 11 to March 16, 1944, with the symptoms described previously. Following this he had several attacks lasting from one hour to three days. For the six days prior to readmission on March 30, 1944, he had experienced no attacks.

On April 4, 1944, while in the hospital, he had another attack. Electrocardiographic tracings revealed typical ventricular tachycardia. Since the patient had not previously responded to quinidine, and because there was a possibility that the origin of the tachycardia was a circus movement about the base of the aorta, perhaps giving a ventricular type of electrocardiographic tracing, it was felt that the tachycardia might respond to supraventricular medication. Therefore mecholyl (acetyl-beta-methyl-choline) was given in the usual dosages without effect. Then 0.6 mg. of lanatoside C were administered intravenously, and within fifteen minutes his cardiac mechanism was restored to normal without any preliminary slowing. Again the patient insisted on going home, therefore we have no further studies as to the effectiveness of lanatoside C.

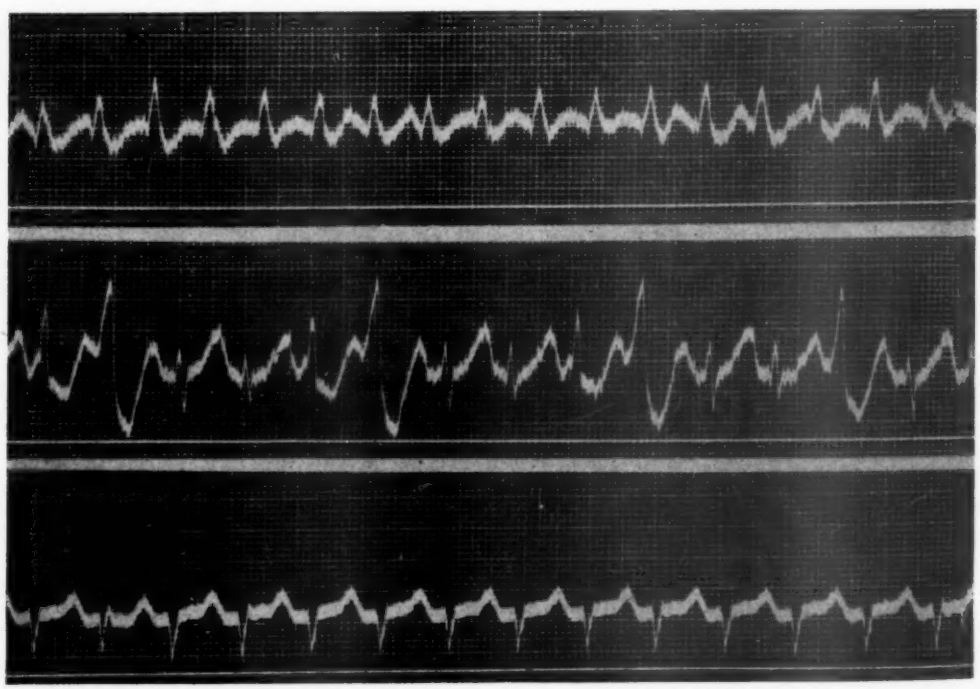

Fig. 5.—Electrocardiographic tracing of paroxysmal auricular tachycardia with premature beats of the ventricle in Lead II, fifteen minutes after the intravenous administration of 0.65 Gm. of quinidine lactate.

DISCUSSION

Ventricular tachycardia may sometimes be anticipated in the earlier days or weeks following a coronary occlusion by the development of multiple ventricular premature beats or by periods of excessively rapid heart beats. In Case 1, whenever the patient began to develop an excessive number of premature beats usually an attack of ventricular tachycardia soon developed.

In ventricular tachycardia, the auricles beat independently of the ventricles but at a slower rate. According to Grieco and Schwartz[6] the rapid

beating of the ventricles may progressively augment the ventricular pacemaker, and thus lead ultimately to asystole. Theoretically, therefore, the cause of death in patients with ventricular tachycardia should be ventricular asystole rather than ventricular fibrillation, and such a mechanism has been found in about one-half of the cases studied at the time of death.[7]

Levine[8] states that it is clinically possible to distinguish ventricular tachycardia from other forms of rapid heart action by the following three points: first, the rhythm is rapid and is essentially regular but slight irregularities can be detected; second, the quality of the first heart sound varies in some of the cycles; third, attempts at vagal or ocular pressure prove ineffective in slowing the tachycardia. Final positive evidence of ventricular tachycardia, however, requires electrocardiographic studies. In our second case (Fig. 5), one episode of tachycardia was auricular in origin; however, the subjective manifestations were no different than in those attacks of ventricular tachycardia. The first electrocardiographic tracings on a case of ventricular tachycardia followed by ventricular fibrillation occurred in an 80-year-old woman and was reported by Reid.[9] Paroxysms of ventricular tachycardia are believed to originate either in the bundle branch tissue or in the muscle of the ventricle. They are characterized, according to Pardee,[10] by typical wide, notched QRS complexes followed by T waves directed opposite to the chief deflection of the QRS group. The P waves may be entirely lost in the large excursions of the ventricular waves, as in our tracings, or the P waves may be discerned occurring in a slower independent rhythm.

The intravenous administration of quinidine lactate is not going to be applicable universally in the treatment of ventricular tachycardia. Our first case, a 52-year-old white man, who had at least two and possibly three attacks of coronary occlusion, experienced eight attacks of ventricular tachycardia proved by electrocardiographic tracings, and each of them was successfully treated with the intravenous administration of quinidine lactate. In the second case, on the other hand, the intravenous administration of quinidine lactate failed to stop any of this patient's attacks of paroxysmal ventricular tachycardia. The tachycardia responded to the intravenous administration of lanatoside C on one occasion, but further studies were not obtained because the patient left the hospital. Prophylactically, the recurrence of the attacks was prevented in the first patient by the oral administration of 30 grains of quinidine sulfate daily. In the second case, on the other hand, recurrences of the attacks continued even with the oral administration of 54 grains of quinidine sulfate daily.

According to Goodman and Gilman,[11] quinidine acts on the heart by increasing the absolute refractory period often as much as 50 to 100 per cent, decreasing the myocardial excitability, and slowing the conduction of impulses in the heart muscle. Drury, Horsfall, and Munly[12] found that quinidine has the same effect on ventricular muscle that it has on the muscles of the auricle. In Levy and Lewis'[13, 14] experiments on cats, it was found that quinidine raised the threshold current for ventricular fibrillation; likewise, the same results were obtained on dogs by Drury, Horsfall, and Munly.[12] Levine and Fulton[15] believe that quinidine not only breaks up the abnormal rhythm but may prevent its return when the condition has a tendency to recur in paroxysms.

Toxic[11] reactions to quinidine are fairly common. Everyone is familiar with cinchonism and its accompanying gastroenteric symptoms, tinnitus, and impaired vision. Idiosyncrasies to the drug in the form of respiratory dis-

tress (occasionally with temporary cessation of respiration), cyanosis, dizziness, nausea, vomiting, and cold sweats occur. The various embolic phenomena that occur with a sudden reversion to a normal mechanism after months of auricular fibrillation, serves as a contraindication to its usage in that condition, but not so to its administration in ventricular tachycardia. Occasionally ventricular standstill, due to the depressant action on the sinoauricular or auriculoventricular nodes, is encountered, and this may be fatal. Death from ventricular fibrillation after quinidine occurs more commonly than is stated.[11]

The administration of quinidine in anticipation of the development of an attack of ventricular tachycardia may prevent it. Scott,[3] in 1922, first demonstrated this effect of quinidine in preventing as well as stopping paroxysms of ventricular tachycardia. His patient was a 39-year-old woman without evidence of organic heart disease. Initially, her attacks were stopped on 0.4 Gm. of quinidine sulfate administered orally three times daily; later she was maintained on 0.2 Gm. daily without recurrence of the attacks. He had also tried digitalis, epinephrine, and glyceryl trinitrate without success in stopping the tachycardia.

Quinidine has been used prophylactically in the prevention of paroxysmal ventricular tachycardia as well as in the treatment of it. Test doses of 3 grains of quinidine sulfate should be given, and during the ensuing twenty-four hours the individual should be observed for any untoward reactions, especially those occurring with idiosynerasy reactions. If these occur, the drug should not be employed. If no reactions occur, however, it is probably safe to administer the drug in the usual doses. As prophylaxis against ventricular tachycardia, 3-grain doses of quinidine sulfate four times daily have been employed. Larger doses may be required, and in some cases it has been necessary to administer as much as 60 grains daily. The first case was adequately controlled without recurrences of ventricular tachycardia on 30-grain doses of quinidine sulfate daily. No toxic symptoms resulted from the administration of the 54-grain doses of quinidine sulfate daily in the second case although it failed to prevent the recurrence of the ventricular tachycardia.

The earliest electrocardiographic change in a patient receiving oral quinidine sulfate is a prolongation of the QRS interval. In one of Gold's[16] patients, receiving a dose of 50 to 60 grains of quinidine sulfate daily, the QRS interval which was originally 0.12 second later became prolonged to 0.16 second and it never went above this; in none of our tracings did the QRS interval become longer than 0.10 second. There is seldom a prolongation of the QRS interval over 0.12 second unless the patient is receiving more than 30 grains of quinidine daily. The cumulation of quinidine ceases in a very few days with a fixed dose and usually after the fifth day the quinidine level reaches its maximum.

The oral administration of quinidine may not control the ventricular tachycardia, and quinidine may have to be administered intravenously as a lifesaving procedure. The patient usually reacts quite violently to the intravenous administration. In our cases it was not uncommon for the patient to feel excessively warm, to have a profuse diaphoresis with a cold, clammy skin, and often rather severe nausea and vomiting. In Case 1 a generalized convulsion occurred concomitantly with the absence of audible heart sounds. Schwartz and Jezer[17] noted that, with the intravenous administration of either quinine dihidrochloride or quinidine sulfate, either a prefibrillation mechanism or transient periods of ventricular fibrillation frequently developed. In their experience, once the prefibrillation mechanism was precipitated by the adminis-

tration of drugs, recurrent periods of transient ventricular fibrillation sometimes followed for several hours. They found also that there was a more rapid appearance of ventricular fibrillation when ventricular premature beats were already present. They, therefore, thought that the usage of quinine and its derivatives was definitely contraindicated for intravenous administration. I have used a preparation of quinidine lactate intravenously in doses varying from 5 to 20 grains. Although moderately severe subjective symptoms were obtained, the ultimate goal of relieving the ventricular tachycardia was reached in many instances, and in none of them did death occur. Perhaps failure to get response to the quinidine either orally or intravenously in the second case was due to the possibility that the origin of the tachycardia was a circus movement about the base of the aorta, perhaps giving a ventricular type of electrocardiographic tracing. On the one occasion in which lanatoside C was administered intravenously, a rather prompt restoration of the normal mechanism occurred. No explanation for this is given, but I have observed this phenomenon following the intravenous administration of lanatoside C in paroxysmal auricular tachycardia in a young child uncontrolled by the methods for treating supraventricular tachycardia.

SUMMARY

Two cases of ventricular tachycardia treated by the intravenous administration of quinidine lactate are reported. The possible etiological factors, diagnostic difficulties, and electrocardiographic findings in ventricular tachycardia are presented. The oral and intravenous administration of quinidine are discussed, also.

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PREMATURE BEATS OF SINUS ORIGIN

Electrocardiographic Demonstration of a Clinical Case

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PREMATURE cardiac systoles have been induced artificially and may theoretically arise physiologically from any portion of the auricles or ventricles, including the A-V node and bundle and, presumably, from the sino-auricular node, also. All varieties of premature beats, *except the last,* are usually readily recognized and demonstrated by ordinary electrocardiographic means. No illustrations of premature beats of sinus origin appear in any of the modern treatises on electrocardiography, and no proved clinical instance seems, thus far, to have been presented in the general medical literature.*

Sinus premature beats may be defined electrocardiographically as premature systoles whose auricular and ventricular deflections in all leads are indistinguishable from those characteristic of the basic sinus rhythm; moreover, the returning cycle following a sinus premature systole should be no longer than the initial cycle. Obviously, premature beats of sinus origin must be differentiated from sinus arrhythmia, from periodic sinoauricular block or auricular standstill, and from certain auricular premature beats; and the acceptability of any case presented as one of sinus premature beats will depend upon how convincingly one may be able to exclude these commoner and more familiar arrhythmias in a case which also meets the established criteria.

The following clinical description concerns a patient who manifested an arrhythmia which we concluded, after particular study, to be due to sinus premature beats.

S. S., a 64-year-old man, had first entered the New Haven Hospital in September, 1942, with empyema in the left side of the chest; this was drained by a thoracotomy, and convalescence was uneventful. In April, 1944, he had a large hematemesis. A history of dysphagia and progressive weakness dating back about sixteen months was obtained. More recently there had been moderate shortness of breath and slight swelling of the ankles. Examination revealed moderate cardiac enlargement, soft aortic and apical systolic murmurs, coupled rhythm with the radial pulse wave of the second beat in each couplet palpably weaker than the first, slight dependent edema, and râles in small numbers at each lung base. The blood pressure was normal (125/65) and there was no ascites or enlargement of the liver. A significant anemia (red blood cells, 3.7 million per cubic millimeter, hemoglobin, 9 Gm.) and hypoproteinemia (5.6 Gm. per cent) were found. Esophagoscopic examination and biopsy disclosed cancer of the esophagus. After transfusion and six days of rest in bed the edema and dyspnea subsided, the murmurs disappeared, but the coupled rhythm persisted without apparent intermission throughout the patient's stay. Treatment was declined, and the patient was discharged after twelve days in the hospital.

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*Sir Thomas Lewis' illustration of a sinus premature systole on page 229 (Fig. 205) of his classical monograph, *The Mechanism and Graphic Registration of the Heart Beat* (London, 1925, Shaw and Sons, ed. 3), shows a single premature beat in but one lead, the premature P wave is, unfortunately, superimposed on the T wave of the preceding cycle, and the successive P waves in the tracing exhibit considerable variation in amplitude. It is difficult, under the circumstances, to accept the essential argument that the premature P wave in question is identical with the P waves of the regular cycles.

The electrocardiogram taken initially to analyze and identify the coupled rhythm is shown in Fig. 1; the diagnosis of coupling due to sinus premature beats was ventured after completion of the special studies that follow.

Our opinion that the coupled rhythm manifested in the case described was due to regularly recurring premature beats of sinus origin was based upon (1) their conforming to the criteria for sinus premature beats, and (2) our ability to exclude the following arrhythmias which intrude on the differential diagnosis.

Simple Arrhythmia of Sinus Origin.—This may be defined as an irregular succession of otherwise normal cardiac cycles. Electrocardiographically, normal auricular deflections are followed after normal A-V conduction times by ventricular complexes, but the successive cycles are unevenly spaced. Two varieties are generally recognized: (1) phasic sinus arrhythmia, which reveals itself in cyclic variations in rate whose periods are obviously related to respiration; holding the breath is generally believed to eliminate this arrhythmia; and (2) nonphasic sinus arrhythmia, in which a respiratory association may not ordinarily be evident but is usually made obvious through the exaggerated influence of deep breathing.

Our case was remarkable in exhibiting coupled rhythm composed of apparently identical auricular and ventricular complexes with only an infrequent and unpredictable momentary interruption of the coupling by the occurrence of three cycles that were very nearly evenly spaced (indicated by brackets in Fig. 1, Lead II). Such persistent bigeminy is not a familiar expression of sinus arrhythmia.

Phasic sinus arrhythmia seemed further excluded because no cyclic variation with respiratory correlation was evident even in strips recorded continuously for more than thirty seconds during normal respiration at a rate of 15 per minute. Moreover, the length of the phases represented by the coupling of the beats was too brief (1.62 seconds) to be correlated with the duration of the respiratory cycles (which averaged about 4 seconds). Finally, the arrhythmia was not abolished by holding the breath (Fig. 1, Lead III).

Nonphasic sinus arrhythmia seemed excluded not only by the practically unvarying constancy of the time relations within and between the successive cycles of coupled beats, but also by the fact that deep breathing abolished rather than exaggerated the arrhythmia during the first seven seconds of the expiratory phase (Fig. 2). Finally, acceleration of the heart rate by mild exertion failed to stop the arrhythmia, as is seen in Fig. 3b, which was recorded after several sit-ups in bed. Moreover, the coupling apparently persisted throughout twelve days of hospitalization during which the patient was allowed full activity on the ward, and during which he exhibited pulse rates varying from 60 to 90. On the basis of this evidence we consider sinus arrhythmia excluded from the differential diagnosis.

Periodic Sinoauricular Block (Auricular Standstill).—Failure of the sinus node to activate the auricles, with resultant nonappearance of a P wave, is usually regarded as due either to increased vagal tone inhibiting the sinoauricular node or depression of the normal pacemaker by drugs, infections, or direct injury. Theoretically, sinoauricular block recurring regularly following two normal cycles could produce coupled rhythm like that illustrated. Another hypothetical situation involving sinoauricular block could be postulated if one assumed that the sinus node might be discharging at twice the rate (every 0.33 second) represented by the short cycles (0.66 second) and that one sinus discharge within the short cycle is blocked. The long cycles would then pre-

Fig. 1.—Standard limb lead electrocardiogram showing uninterrupted coupled rhythm in Leads I and III, while in Lead II the coupling is interrupted twice (within brackets) by two cycles of apparently normal sinus rhythm. Breath was held during the recording of Lead III.

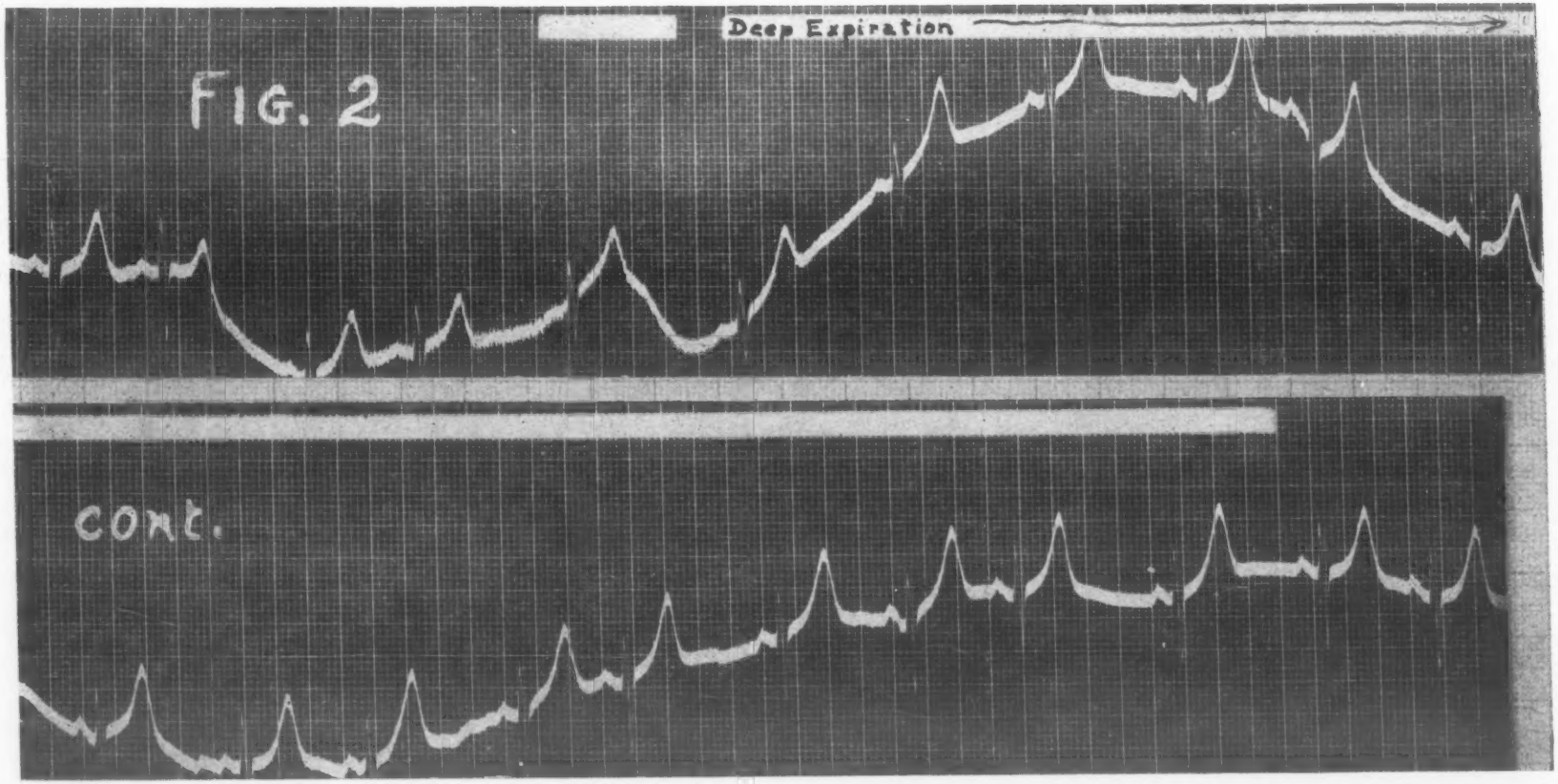

Fig. 2.—Semidirect electrocardiogram obtained from chest wall with right and left arm electrodes over third and fifth intercostal spaces, respectively, adjacent to sternal margin. During sustained expiration, indicated by white stripe, the coupled rhythm was abolished for seven seconds.

sumably result from the blocking of two successive sinus discharges. The long cycles should, under these circumstances, be 0.99 second apart. Actual measurement of the P-R intervals of the long cycles in Fig. 3*a* and 4, which offers the advantage of amplified auricular deflections for precise measurement, does in fact yield almost exactly, but perhaps fortuitously, this predicted value (actually 0.96 second). However, to accept the hypothesis as proved by this argument it becomes necessary to accept a fundamental sinus discharge rate of 182 per minute as implied by the assumed cycle length of 0.33 second. It appeared hazardous to invoke two extraordinary disturbances in rhythm to explain the bigeminy in this case, particularly since the diagnosis of sinoauricular block, whether with or without the hypothetical tachycardia, seemed untenable from the following observations:

1. S-A block presents itself usually as isolated dropped beats occurring irregularly, or as more sustained periods of auricular standstill, and not as a regularly intermittent phenomenon with the production of coupled rhythm.

2. The usual toxic influences (digitalis, quinidine, infections) which produce S-A block were not present.

3. Failure of the arrhythmia to be diminished or abolished by a "sympathicotonic" influence like exercise (Fig. 3*b*) is atypical behavior for S-A block.

4. The temporary abolition of the arrhythmia by a "vagotonic" influence like deep expiration following a full inspiration (Fig. 2) is contrary to the behavior of S-A block which should be intensified by such a maneuver.

Sinoauricular block appeared excluded from the differential diagnosis by the considerations mentioned.

Auricular Premature Systoles.—The fundamental electrocardiographic characteristics of this irregularity are a premature P wave that usually differs at least slightly in form from the subject's normal or natural auricular deflection, and a P-R interval at least 0.12 second long, and usually as long or longer than the average A-V conduction for the subject. The nearer the ectopic auricular focus lies in relation to the sinus node, the closer may be the resemblance of the auricular phenomena recorded electrocardiographically from the normal and the abnormal focus.

Careful inspection of the P waves and P-R intervals throughout each of the three standard limb leads (Fig. 1) reveals no detectable differences, however minor, in the course of any one lead. This implies that the auricular waves in each couplet have a common site of origin, and since the P waves throughout are of normal configuration, amplitude, and direction, the designation of a sinus origin for the premature beats seems warranted.

It must be acknowledged that, under circumstances of extreme adjacency of an ectopic auricular focus and the sinus node, the P waves resulting from auricular excitation in each instance (and their P-R intervals) may be remarkably similar. However, minor changes in the appearance of the P waves may theoretically be expected, even when the site of the impulse formation is shifted within the sinus node; and it is conceivable that very slight differences may not be recorded by the peripheral limb leads of conventional electrocardiographic technique, which admittedly reproduces the auricular deflection relatively inadequately as a small monophasic deflection instead of as a complex of two or more phases that are revealed by direct leads.

In order, therefore, to investigate the details of the P waves and P-R intervals more precisely in our case and to verify their identity or reveal slight differences, we obtained semidirect leads from the chest wall and then further ampli-

Fig. 3a.—Amplified electrocardiogram obtained by placing right and left arm electrodes over third and fifth intercostal spaces, respectively, adjacent to right sternal margin, and amplified about fourteen times; 3b, same, after mild exercise.

Fig. 4.—Amplified electrocardiogram obtained by placing right and left arm electrodes over third right and left intercostal spaces, respectively, adjacent to sternal margin.

fied the resulting electrocardiogram. This was done by placing the arm lead electrodes in contact with the chest wall in the third and fifth intercostal spaces at the right margin of the sternum, and also in the third intercostal spaces at the right and left margins of the sternum. The right arm terminal and electrode in either placement occupied the upper or the right-sided position. Further amplification of the resulting augmented deflections was obtained by interposing a single-stage resistance-coupled amplifier, described previously,[1] in the lead line between the patient and the electrocardiograph.* The auricular deflections so obtained were about fourteen times larger than those recorded by the limb leads and, as expected, they exhibited a more complex and diphasic character permitting more detailed study (Figs. 3 and 4).

Inspection of these amplified P waves again revealed a remarkable identity in form within each couplet. Such minor differences as could occasionally be discovered were found to prevail also between the P wave contours of successive beats whether in the premature or normal position; they were probably slight artefacts resulting from the high amplification. Moreover, the P-R intervals, which permitted exceptionally precise measurement in the amplified records, also proved to be remarkably similar in differing only occasionally and by not more than 0.02 second throughout the records. Finally, to exclude the possibility that the premature cycle might arise from an extrasinus focus which happened to be exactly the same distance from the A-V node as the S-A node for the chosen (vertical) plane of the lead-off points, amplified electrocardiograms were repeated for the opposite (horizontal) plane; these records also verified the constancy of the A-V conduction time for the normal and premature cycles and again revealed the identity of P-wave contour for the two auricular deflections in each couplet.

These observations, fortified by the evidence obtained from the amplified electrocardiograms, seem to establish that the premature beats arose within the sinus node, and that their precise point of origin was identical with the site of the normal pacemaker in this case.

COMMENT

The cause of the sinus premature beats in our case was not evident. The patient was not critically ill, his nutritional state was good, and the only objective finding of possible cardiovascular interest was transient edema of the ankles and a moderate anemia. The alleviation of the anemia with two transfusions, which restored the hemoglobin level to 12 Gm. (78 per cent), did not apparently affect the arrhythmia. The only medications included moderate doses of aspirin for five days, and an almost nightly soporific of pentobarbital (0.1 Gm.), a single dose of morphine (0.01 Gm.) in preparation for esophagoscopic examination, and moderate daily doses of thiamine and of vitamin B complex (brewers' yeast). None of these medications could conceivably have induced the constant arrhythmia. From bronchoscopic and roentgenographic examinations there was no evidence that the esophageal cancer had infiltrated the mediastinum, there was no clinical indication of pericardial effusion, and there was no deformity of the contour of the heart in the roentgenograms to suggest invasion by cancer.

SUMMARY

An elderly man with cancer of the esophagus presented coupled rhythm apparently continuously during twelve days of observation, and electrocardio-

*"Cardiette," Sanborn Company.

graphic study employing auricular amplification techniques led to the diagnosis of regularly recurring premature beats of sinus origin. To our knowledge, this is the first convincing demonstration of sinus premature beats occurring clinically. The cause for the arrhythmia was not apparent.

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INCOMPLETE HEART BLOCK PRODUCED BY CHANGES IN POSTURE

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THE relation of second degree heart block to posture was brought to our attention by the first of our cases listed below. Shortly afterward a case of first degree heart block was noted in routine examination, and when studied the P-R interval was found to vary with posture. In both of these cases heart block was abolished when the subject assumed the upright position. A third case, one of first degree heart block in which the block was not influenced to a major degree by posture, is included for comparison.

Review of the literature has revealed one case reported by Alexander and Bauerlein[1] in which heart block was observed in the supine position and disappeared in the standing position. Poel[2] reported a case of first degree heart block which showed variations of P-R interval with posture. Poel[2] also cites three cases of vagal effect on incomplete heart block from the literature, but the effects of posture were not given.

REPORT OF CASES

CASE 1.—The patient was a white man, aged 22 years. During routine altitude indoctrination on May 5, 1944, in a low-pressure chamber this man suffered "bends" at a simulated altitude of 30,000 feet. During descent to ground level the subject was in a sitting position, and the character of the pulse was weak, rhythmic, and regular. Upon reaching ground level he was transferred to a bed and placed in the supine position. When examined in this position the pulse exhibited weakness, arrhythmia, and irregularity in that there was a dropping of every third to fourth beat. The pulse rate at that time was 78 per minute. The blood pressure was 130/76. After an hour of rest in bed and the administration of oxygen at the rate of 6 liters per minute the subject was allowed to stand. Since the pulse was rhythmic and regular, and the blood pressure was 122/70 while he was in the standing position, the soldier was considered free from any ill effects of aero-embolism and was therefore returned to duty. Three days later a recheck of simulated altitude flight was made. Again the soldier suffered from "bends" at 30,000 feet and was brought quickly to ground level. Examination on descent in the escape-lock showed the pulse to be rhythmic and regular (rate, 72 per minute), but on placing the subject in the supine position irregularity of the pulse with dropped beats was noted. An electrocardiogram was made in the supine position at that time (Fig. 1). After an hour of rest in bed and oxygen therapy the patient was permitted to stand, and the pulse was noted to have lost its irregularity and arrhythmia. In the absence of any other cardiac symptom or sign it was suspected that the above irregularity was on a postural basis. This was confirmed when it was found that the irregularity could be reproduced at will by placing the subject in the supine position and that on standing or sitting the pulse again became regular. The soldier was discharged to duty but ordered to return daily so that he could be observed. During each visit the electrocardiographic tracings were repeated in the supine, sitting, and standing positions (Fig. 2).

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Past Medical History.—The patient had had the usual childhood diseases. There was no history of rheumatic fever, scarlet fever, or diphtheria. Tonsillectomy and adenoidectomy were performed at the age of 6 years. Fracture of the nose had occurred at the age of 8 years, with plastic operation on same at the age of 20. At the age of 15 years he was struck in the left eye with a potato fork; this resulted in loss of vision in the eye without loss of the globe. At the age of 17 years he sustained "steering-wheel" compression of the chest, but no fracture of the ribs or sternum. Family and marital histories were negative. System history was negative.

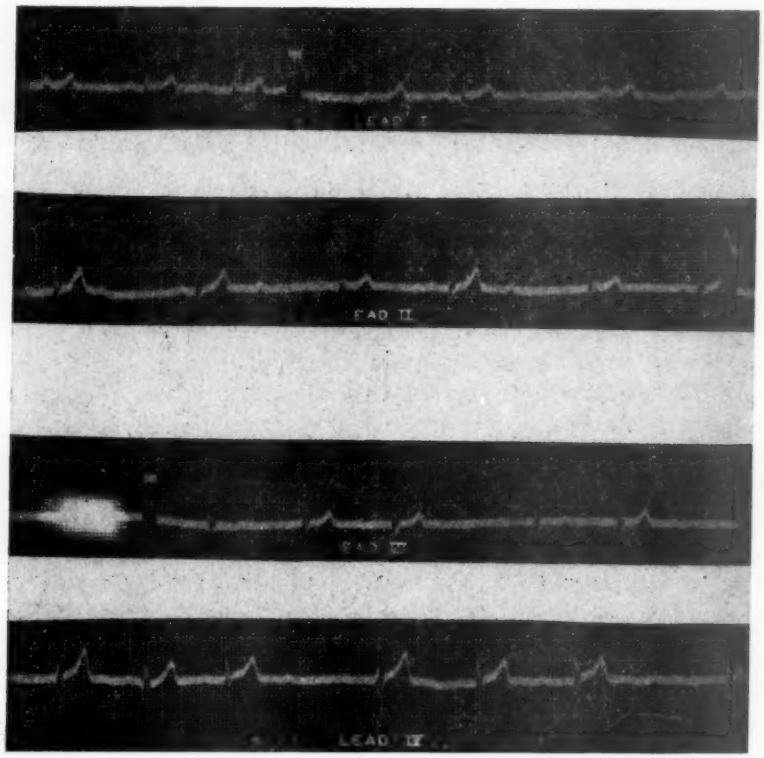

Fig. 1.—Electrocardiographic tracing of Case 1 made in supine position thirty minutes after descent from simulated altitude of 30,000 feet in low presure chamber (May 8, 1944) showing Wenckebach phenomenon. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

Physical Examination.—Height, 72½ inches; weight, 173 pounds; head, negative; ears, negative; eyes, O. D. 20/20, O. S. 20/800, pupils equal, O. D. reacted to light and in accommodation, O. S. sluggish to light, extraocular movements normal; nose, negative; mouth, teeth in fair condition; chest, lungs clear; heart, not enlarged, sounds of good quality, no murmurs; abdomen, negative; extremities, negative; neurological examination, negative. Laboratory examination: Kahn, negative; urinalysis, negative; x-ray of chest including fluoroscopy of the heart in the supine and upright positions and examination of the esophagus and cardiac shadow with the aid of contrast media revealed no gross abnormality. No true intrinsic lesion or intraluminal lesion of the esophagus could be observed. The cardiac silhouette appeared rather globular, but was considered to be within normal limits. No evidence of chamber enlargement could be discerned.

Electrocardiographic Examinations.—The first tracings, taken in the supine position (Fig. 1), show an auricular rate of 75 and a ventricular rate of 54. The P-R interval increases progressively from 0.16 to 0.36 second, and is followed by a P wave without a ventricular complex. The next ventricular complex is of abnormal contour. In some phases it is preceded by a P-R interval of less than 0.12 second, or the P wave may be superimposed on the QRS complex (lower nodal rhythm). Three days later tracings were made in various positions with the results as follows (Fig. 2): Standing position (Fig. 2, *A*), normal electrocardiogram with auricular and ventricular rates of 79 and P-R interval of 0.20 second.

Immediately upon assuming the supine position (Fig. 2, *B*) there is a transition from the normal electrocardiogram to one exhibiting Wenckebach phenomenon. The electrocardiogram taken after a period of time in the supine position (Fig. 2, *C*), shows Wenckebach phenomenon with ventricular escape. The P-R interval progresses from 0.16 to 0.36 second. Some of the complexes of ventricular escape show superimposed P waves similar to those seen in Fig. 1.

Tracings made in the sitting position were similar to those made in the standing position. In both the supine and standing positions, carotid sinus pressure and eyeball pressure had no effect. Tracings made on the stomach, back, and either side were identical. Sleep did not abolish the Wenckebach phenomenon. All the above studies were repeated fourteen and eighty-three days later, and the results were identical. Further electrocardiographic studies were made under 1/50 grain of atropine, given subcutaneously, on Aug. 31, 1944. The drug completely abolished the increased P-R interval and the Wenckebach phenomenon. The P-R interval was 0.16 second, and the heart rate 100 per minute. The effect of exercise was studied and was found to be dependent upon the degree of exertion. Immediately following exercise the subject was placed in the supine position and tracings were made. The increased P-R interval and Wenckebach phenomenon were unaffected by mild exercise, but abolished by vigorous exercise.

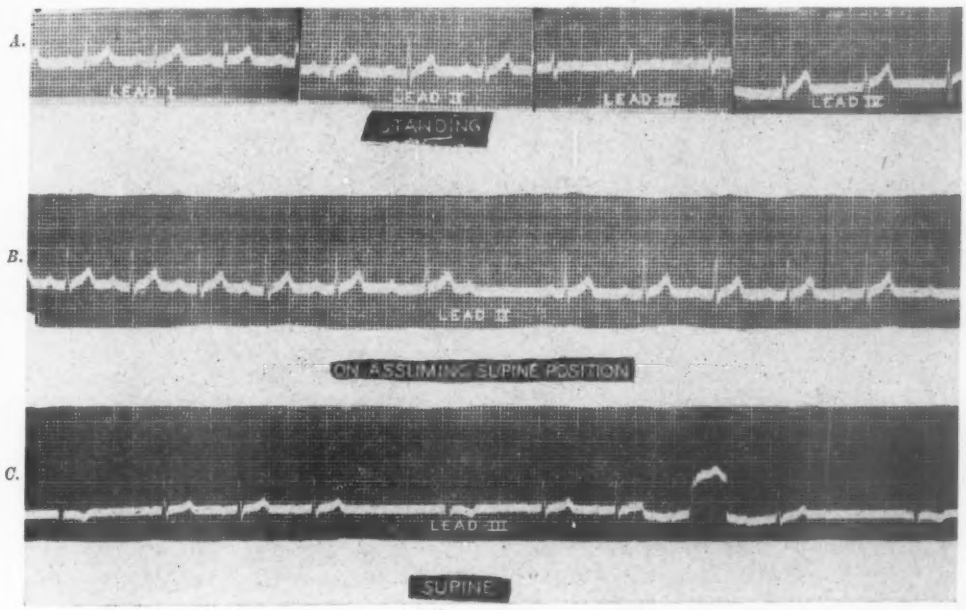

Fig. 2.—Electrocardiographic record of Case 1 showing tracing made *A*, in standing position, *B*, on assuming supine position, and *C*, after a period of time in supine position. *B* and *C* show Wenckebach phenomenon, and *C* also shows ventricular escape. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

Case 2.—The patient was a white man, aged 22 years. During routine electrocardiographic study for duty as inside observer in an altitude chamber, it was noted that this man exhibited a P-R interval of 0.40 second. Questioning revealed no symptoms referable to the cardiovascular system, and in supervised exercise he was equal to other members of his unit. Because of the interest aroused by the previous case (Case 1) similar studies were carried out on this man.

Past Medical History.—The past medical history was essentially negative except for childhood diseases, appendectomy, tonsillectomy, and adenoidectomy. Marital and family histories were not contributory.

Physical Examination.—Height, 68½ inches; weight, 150 pounds; head, negative; eyes, 20/20 vision bilaterally, pupils equal, react to light and in accommodation, extra-ocular movements normal; ears, normal, hearing 20/20 bilaterally; nose, normal; teeth, fair; nasopharynx, normal; tonsils, enucleated; lungs, clear; heart, not enlarged, sounds of good quality, no murmurs, pulse 72 per minute, blood pressure 118/76; abdomen, negative; genitourinary system, negative; extremities, negative; neurological examination, negative. Labora-

tory examination: Kahn, negative; urinalysis, negative; blood counts within normal limits. Special radiological examination showed the cardiac silhouette within normal limits and no abnormalities of the mediastinum and esophagus.

Electrocardiographic Examination.—The first tracings taken in the supine position (Fig. 3, *A*), show an auricular rate of 79 and a ventricular rate of 79. The P-R interval is 0.40 second. Records taken in the *supine position immediately after exercise* (Fig. 3, *C*) (two-step exercise of Masters and Oppenheimer[3]), showed a heart rate of 75 and P-R interval of 0.19 second. With the subject in the supine position, pressure was applied to the right carotid sinus. The tracing (Fig. 3, *D*) showed the heart rate to slow from 75 to 62 and the P-R interval to decrease from 0.37 to 0.17 second. Similar changes were exhibited by eyeball pressure. Observations made in the supine position after atropine (1/50 grain subcutaneously) showed a decrease of the P-R interval to 0.20 to 0.21 second in all records where there was an increased cardiac rate.

Tracings made in the sitting position were similar to those made in the standing position, and showed a normal P-R interval of 0.16 second (Fig. 3, *B*). Tracings made while on the stomach, on either side, or supine were identical. All studies were repeated over a period of twenty days.

Fig. 3.—Electrocardiographic tracings of Case 2, showing *A*, prolonged P-R interval in supine position, *B*, normal P-R interval in standing position, *C*, normal P-R interval in supine position immediately after exercise, and *D*, decrease of P-R interval following right carotid sinus pressure as noted in last two cardiac cycles. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

CASE 3.—The patient was a white man, aged 27 years. During routine electrocardiographic study for duty as inside observer in an altitude chamber on Sept. 4, 1943, it was noted that this man exhibited a P-R interval of 0.40 second. Questioning revealed no symptoms referable to the cardiovascular system, and, like the preceding cases, his exercise tolerance showed him equal to other members of his unit. Because of the interest aroused by the preceding cases this man was re-examined and studied in a similar manner.

Past Medical History.—He had had the usual childhood diseases including diphtheria and scarlet fever. There was no history of rheumatic fever. Tonsillectomy and adenoidec-

tomy had been performed when he was 5 years old. He had suffered a fractured nose in 1936. Family and marital histories were not contributory.

Physical Examination.—Height, 70 inches; weight, 152 pounds; head, negative; eyes, vision 20/20 bilaterally, pupils equal and react to light and in accommodation; ears, negative, hearing 20/20 bilaterally; nose, normal; teeth, fair; lungs, clear; heart, not enlarged, sounds of good quality, no murmurs, pulse 64 per minute, blood pressure 108/58; abdomen, negative; genitourinary system, negative; extremities, negative; neurological examination, negative. Laboratory examination: Kahn, negative; urinalysis, negative; blood counts within normal limtis. Radiological examination showed the heart normal in size and shape and the mediastinum and esophagus within normal limits.

Electrocardiographic Examination.—Tracings (Fig. 4, *A*) taken in the supine position on Aug. 24, 1944, show a heart rate of 62 and a P-R interval of 0.36 second. The P waves and QRS complexes are normal. There is a slight elevation of the S-S-T_2 segment. Tracings made in the standing position show a rate of 81 per minute and the P-R interval is 0.28 second (Fig. 4, *B*). The S-S-T_2 segment is slightly elevated and the T_2 is diphasic. A tracing made after performance of the two-step exercise of Masters and Oppenheimer[3] shows a P-R interval of 0.28 second. A tracing made after right carotid sinus pressure shows a heart rate of 36 per minute (control rate, 62 per minute), and the P-R interval changed from 0.36 second to 0.28 second (Fig. 4, *C*). In no tracing in this study were there any dropped beats. A tracing made in the supine position after the administration of atropine (1/50 grain subcutaneously) showed reduction of the P-R interval from 0.36 to 0.28 second and a heart rate of 79 (control rate, 68).

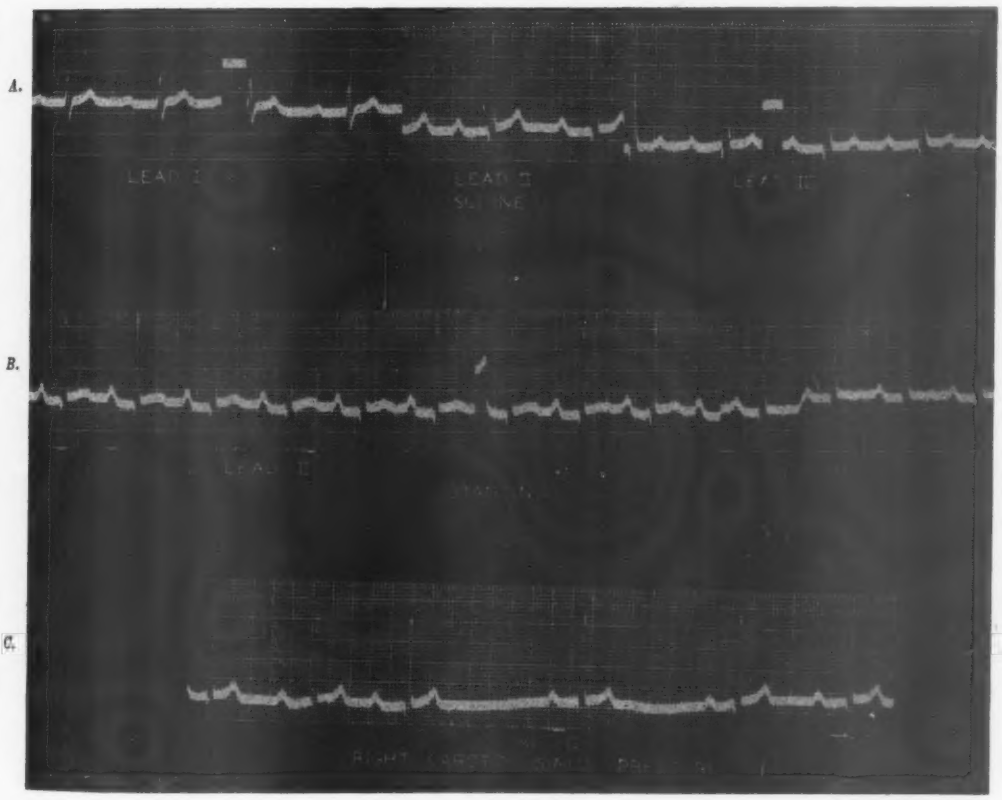

Fig. 4.—Electrocardiographic tracings of Case 3, showing *A*, prolonged P-R interval in supine position, *B*, prolonged P-R interval in standing position, and *C*, effect of right carotid sinus pressure. (Photo by U. S. Army Air Forces, Flying Training Command, Buckingham Army Air Field, Fort Myers, Florida.)

DISCUSSION

The important features of these cases are listed in Table I. In all three cases there was marked prolongation of the P-R interval in the supine position. (In Case 1, the P-R interval increased progressively from 0.16 to 0.36 second,

TABLE I. A COMPARATIVE STUDY OF CHANGES IN P-R INTERVAL IN THE THREE CASES REPORTED

	CASE 1	CASE 2	CASE 3
AGE (YRS.)	22	22	27
SUPINE	Heart rate: auricular, 75; ventricular, 54. Progressively increasing P-R interval, 0.16 to 0.36 second	Heart rate, 79. P-R interval, 0.36 to 0.40 second	Heart rate, 62. P-R interval 0.36 second
STANDING	Heart rate: auricular, 79; ventricular, 79. P-R interval, 0.20 second	Heart rate, 79. P-R interval 0.16 second	Heart rate, 81. P-R interval 0.28 second
WENCKEBACH PHENOMENON WHEN SUPINE	Present	Not present	Not present
ATROPINE (SUPINE POSITION)	Heart rate: auricular, 100; ventricular, 100. P-R interval, 0.16 second	Heart rate, 100. P-R interval, 0.20 to 0.21 second	Heart rate, 79. P-R interval 0.28 second
CAROTID (RIGHT) SINUS PRESSURE (SUPINE POSITION)	No change	Heart rate, 62. P-R interval 0.17 second	Heart rate, 36. P-R interval 0.28 second
EYEBALL PRESSURE (SUPINE POSITION)	No change	Heart rate, 62. P-R interval 0.17 second	No change
TWO-STEP EXERCISE (SUPINE POSITION)	Heart rate, 71. P-R interval, 0.16 second	Heart rate, 75. P-R interval 0.19 second	Heart rate, 80. P-R interval 0.28 second

with Wenckebach phenomenon; in Case 2, the P-R interval was 0.36 to 0.40 second; and in Case 3, the P-R interval was 0.36 second.) On standing the P-R interval of the first two cases returned to normal limits while the third dropped to 0.28 second.

The characteristic sequence of lengthening of A-V conduction time with eventual dropping of a ventricular beat was first described by Wenckebach.[4] This phenomenon was noted in only one of our cases. (In Case 1 the P-R interval increased progressively from 0.16 to 0.36 second, with dropping of ventricular beat.)

In order to evaluate the vagal influence in these cases, atropinization (1/50 grain subcutaneously) was done. In the first two cases the prolonged P-R intervals were restored to normal limits (Case 1, P-R interval 0.16 second; Case 2, P-R interval 0.20 to 0.21 second). In the third case the P-R interval did not return to normal limits (Case 3, P-R interval 0.28 second). However, one must view with caution the concept that positional change followed by a decrease in P-R interval is completely one of variations in vagal influence. The records show that the reduction of P-R interval with change in posture can occur without change in rate.

Studies were made on the effect of right carotid sinus and eyeball pressure. In Case 2 the P-R interval changed from 0.37 to 0.17 second; in Case 3 the P-R interval dropped from 0.34 to 0.28 second. There was no change in Case 1.

The subjects were exercised according to the two-step exercise of Masters and Oppenheimer;[3] immediately afterward they were placed in the supine position, and electrocardiographic tracings were made. In Cases 1 and 2 the P-R interval was within normal limits (Case 1, P-R interval 0.16 second; Case

2, P-R interval 0.19 second). Exercise of a lesser degree than the "two-step exercise" in Case 1 showed no effect on the Wenckebach phenomenon. In Case 3 the P-R interval decreased from 0.36 to 0.28 second.

Our three cases have been those of healthy adult males, able to carry on full military activity, and free of any cardiac symptoms. Their discovery was on routine basis. In Case 3 the finding of first-degree heart block was apparent in any position. However, in the other two cases, physical and electrocardiographic studies done in the sitting or standing positions would have been negative, whereas in the supine position both showed positive electrocardiographic findings, and one showed a physical sign. Our experience with these two subjects suggests that, for proper evaluation, all cases of first and second degree heart block should be examined in both the upright and supine positions.

In consideration of the data in Case 3 it is our opinion that, in this instance, the physiologic lower limit of A-V conduction time is 0.28 second. This conclusion is based on our finding that atropinization, carotid sinus and eyeball pressure, exercise, and standing will not reduce the P-R interval below 0.28 second. In Cases 1 and 2, A-V conduction time can be lowered to within normal limits by standing, by atropinization, by exercise and, in Case 2, by carotid sinus and eyeball pressure. Evidence from these two cases suggests that the P-R interval can have a wide physiologic range.

Data from three somewhat similar cases reported in the literature are summarized in Table II. It will be noted that Alexander and Bauerlein[1] thought their case to be one of early heart block of organic etiology whereas the other two cases were in organically sound hearts. In only two of the cases was the postural effect on the P-R interval studied, and in both there was a decrease similar to that in our Case 3, but it did not return to normal limits as in our Cases 1 and 2. After exercise and in a supine position two of the cases showed a P-R interval within normal limits while the third showed Wenckebach phenomenon with prolonged P-R interval. Atropine was given in only two cases and in both instances abolished the A-V block.

TABLE II. A COMPARATIVE STUDY OF CHANGES IN P-R INTERVAL IN THE THREE CASES REPORTED IN THE LITERATURE

	POEL[2]	LEVY[5]	ALEXANDER AND BAUERLEIN[1]
AGE (YRS.)	15	14	64
SUPINE	Heart rate, 81. P-R interval 0.36 second	Heart rate, 86. Control P-R interval 0.26 second. Position not given	Heart rate: auricular, 62; ventricular, 35.5. P-R intervals increasing progressively from 0.2 to 0.4 second
STANDING	Heart rate, 74. P-R interval 0.30 second		Heart rate: auricular, 71; ventricular, 71. P-R interval 0.28 second
WENCKEBACH PHENOMENON	Absent	Present	Present
ATROPINE	Not given	A-V block abolished	Heart rate: auricular, 80; ventricular, 80. P-R interval 0.24 second
CAROTID SINUS PRESSURE	–	Not given	Not given
EYEBALL PRESSURE	–	–	–
EXERCISE	Heart rate, 90. P-R interval 0.18 second	Heart rate, 86. P-R interval 0.18 second	Heart rate: auricular, 80; ventricular, 75. P-R interval 0.22 to 0.32 second

SUMMARY

1. Two cases are presented to show that first and second degree heart block can be produced by change in posture from the upright to the supine.

2. The data show that in two of our cases a decrease of P-R interval will occur with change in posture but without a concomitant change in rate (Table I).

3. The effects of atropine, exercise, and carotid sinus and eyeball pressure have been studied in these cases.

4. A review of the literature and comparison with our cases has been made.

5. It is suggested that all cases of incomplete heart block be studied for postural evaluation.

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Clinical Reports

UNUSUAL PRIMARY LEIOMYOSARCOMA OF THE HEART

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PRIMARY tumor of the heart is rare. The following case is reported not only because of its interest as a case of leiomyosarcoma primary in the heart, but also for the reason that we feel the many observations and recordings contained within this protocol will be of value to clinicians in making a differential diagnosis between tumor of the heart and ventricular aneurysm following myocardial infarction. This case was erroneously diagnosed clinically as the latter. We were fortunate enough to have been given the opportunity of following this patient from a point very early in the course of his disease to the autopsy table, a period of approximately four and one-half months.

CASE REPORT

The patient, a 34-year-old white man, was first admitted to the Station Hospital, Fort Ord, California, on April 16, 1943, complaining of sharp, stabbing pain in the left upper abdomen; this pain was of approximately four weeks' duration. His general appearance at this time was good, although he was admitted to the ward in a wheel chair.

His past and family histories were irrelevant. In his personal history he admitted to the moderate use of tobacco.

His present illness began on March 20, 1943, while the soldier was on a scheduled 25-mile hike. After completing about 5 miles of the hike he was overtaken by a "choking up" sensation and had to fall out. He had no actual substernal pain but experienced a sensation as if he had "run a great distance."

For three days following, his temperature was 100° F., and on March 24, 1943, he was admitted to the Station Hospital, Camp McQuaide, California, where a diagnosis of pericarditis was made. A pericardial friction rub was heard at the time of admission and persisted for a period of ten days. Admission laboratory data at Camp McQuaide consisted of the following: red blood cells, 4,230,000; white blood cells, 14,800, with a normal differential; and hemoglobin, 70 per cent. Temperature returned to normal the day following admission to Camp McQuaide Hospital and remained normal thereafter. A chest roentgenogram taken April 8, 1943, revealed an enlarged left ventricle (Fig. 1, *A* and *B*). The white blood cell count at that time was 9,500, with a normal differential; red blood cell count, 4, 850,000; and hemoglobin, 14.5 grams. His urine was normal; sedimentation rate was 19 mm. in one hour.

He was transferred to the Station Hospital, Fort Ord, California, on April 16, 1943. He was seen by the cardiologist who made an admitting provisional diagnosis of pericarditis subsequent to an acute arteritis with myocardial infarction. The electrocardiogram at the time of admission showed evidence of pericarditis with a possible myocardial infarction (Fig. 2). Physical examination at the time of admission was negative except as related to the heart.

The point of maximum intensity of the cardiac beat was in the fifth intercostal space just lateral to the nipple line. Heart sounds were of fair quality; no murmurs or friction rub was heard. The pulse rate was 80 per minute, and the blood pressure was 130/70. Initial treatment consisted largely of rest in bed.

Because of enlargement of the left ventricle noted on the roentgenograph of the chest taken April 8, 1943, fluoroscopic examination was done several days following admission to this hospital which revealed the enlargement of the heart to involve only the apical portion of the left ventricle. Pulsations were normal in all portions of the heart except in this region where they were seen to be extremely weak.

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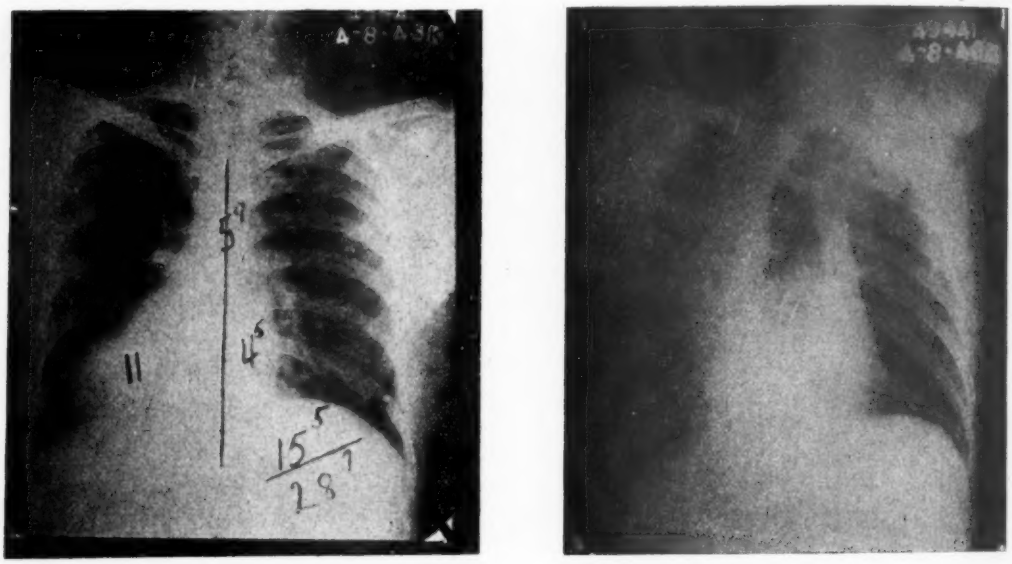
By May 1, 1943, the sedimentation rate had returned to normal, and he was relatively asymptomatic. Despite repeated electrocardiograms showing evidence of persistent myocardial damage, the patient progressed in a relatively asymptomatic manner. A roentgenograph of the chest taken May 8, 1943, showed further enlargement of the left ventricle (Fig. 3). Repeat fluoroscopic study revealed very feeble pulsations of the entire left ventricle; this observation was corroborated by kymographic tracings. He was still asymptomatic but spent most of the time in bed or walking about the ward.



A. *B.*

Fig. 1.—*A*, Posteroanterior 6-foot roentgenogram of the chest taken April 8, 1943, showing moderate enlargement of the left ventricle. *B*, Left anterior oblique 6-foot projection of the chest taken April 8, 1943, showing enlargement of heart to be confined to the region of the left ventricle.

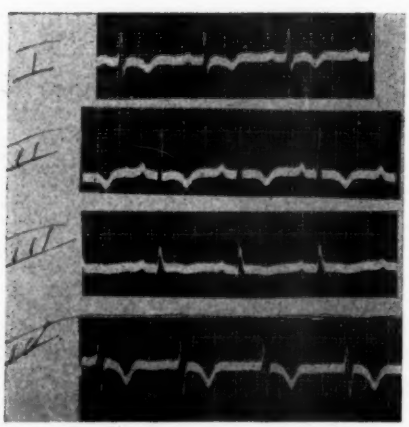


Fig. 2.

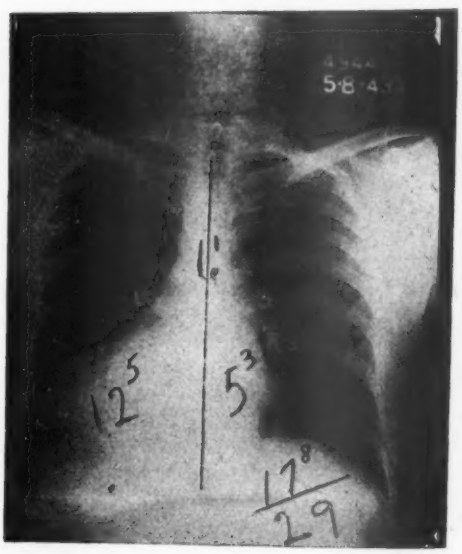


Fig. 3.

Fig. 2.—Electrocardiogram taken April 16, 1943, showing negativity of T waves in all leads with slight slurring of R_S. No RS-T elevation or depression but slight coving S-T_1. Lead IV standard IVF.

Fig. 3.—Posteroanterior 6-foot roentgenogram of the chest taken May 8, 1943, showing further enlargement of the left ventricle with the cardiac shadow beginning to show the so-called "boot shape."

On June 4, 1943, his venous pressure was determined as 9 cm. (normal 3 to 8 cm.), and his circulation time was 17 seconds (normal 15 to 18 seconds).

On June 9, 1943, he first noted the appearance of orthopnea at nighttime which required the use of an extra pillow for comfortable sleeping. At this time there was noted a short, sharp, harsh, systolic, aortic murmur. The heart rate at this time was 100. The lungs were clear to auscultation, but a mild cardiac decompensation was apparent clinically. The heart murmurs were interpreted as being functional in nature and due to cardiac dilatation.

Roentgenographs of the chest on this date revealed further enlargement of the heart, the left border of which reached the lateral chest wall; the total transverse diameter now measured 19.9 cm. (Fig. 4). The cardiac murmur persisted, and the pulse rate now reached

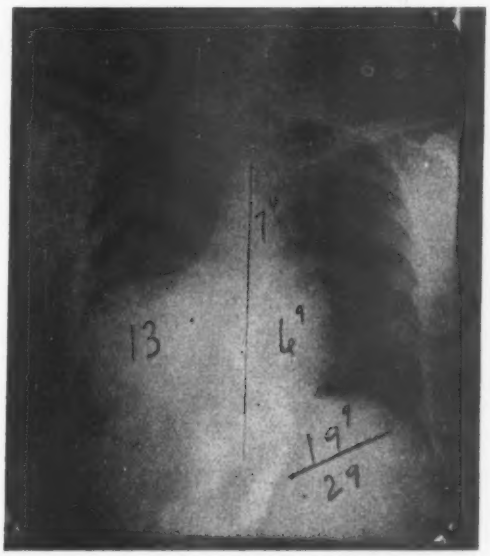
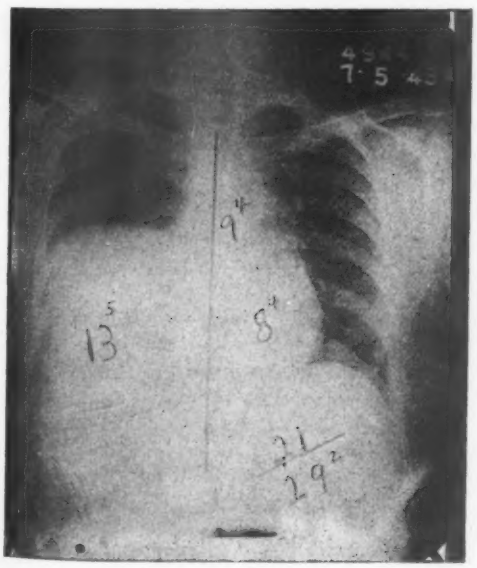
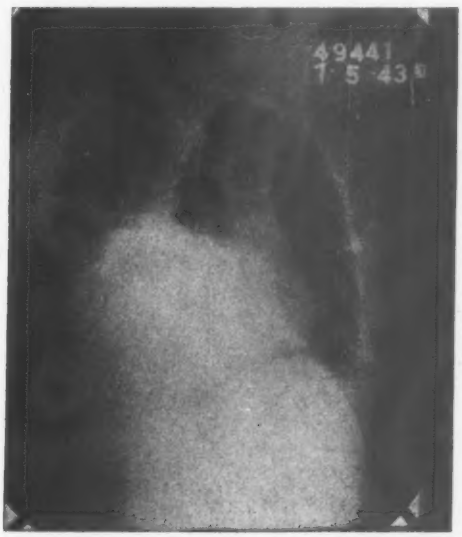


Fig. 4.—Posteroanterior 6-foot roentgenogram of the chest taken June 9, 1943, showing still further enlargement of the left ventricle area, the left border of the heart touching the lateral wall of the thorax. Also there is beginning enlargement towards the right.



A.



B.

Fig. 5.—*A*, Posteroanterior 6-foot roentgenogram of chest taken July 5, 1943, showing even greater enlargement of the heart. The mediastinum appears displaced slightly toward the right. The heart has assumed the "boot shape." *B*, Left anterior oblique 6-foot projection taken July 5, 1943, showing the enlargement of the heart to be confined apparently to the left ventricle.

108 beats per minute. His venous pressure on June 12, 1943, was 13.5 cm., and his circulation time had increased to 31.2 seconds.

By June 16, 1943, his cardiac decompensation was greater with the presence of a moderate amount of dependent pitting edema. Digitalization was instituted following which his pulse rate dropped to 84 beats per minute. His orthopnea, however, remained, and the total transverse diameter of the heart now increased to 20.6 centimeters. Soon following, it was noticed that he was beginning to have what appeared to be an icteric tinge to his sclerae, but an icterus index revealed only 7.5 units of bilirubin.

By June 28, 1943, his decompensation had improved somewhat, although his peripheral edema persisted, and he had but slight difficulty in breathing at nighttime. Blood counts at this time revealed his red blood cell count to be 3,820,000 and his hemoglobin to be 10.5 Gm., as compared to an admission red blood cell count of 4,580,000 and a hemoglobin of 14.5 grams. His urine, which on admission had been entirely normal, now contained 3 plus to 4 plus albumin, an occasional pus cell, and a few casts of all types. His general condition appeared worse.

On July 5, 1943, radiographs of the chest revealed the left border of the heart to extend completely to the lateral wall of the chest with apparent displacement of the heart to the right, including the lower end of the trachea and right main bronchus (Fig. 5, *A* and *B*). There had also occurred some increase upward in the position of the left border of the heart so that its left upper border lay transversely, producing a so-called boot-shaped appearance of the heart. The total transverse diameter of the heart was 21.9 centimeters. Several days later his decompensation became severe with a marked pitting edema of both lower extremities with a large amount of fluid in the peritoneal cavity.

On July 2, 1943, his total serum proteins were found to be 6.5 Gm., with 4.1 Gm. of albumin and 2.4 Gm. of globulin per 100 cubic centimeters.

With the use of diuretic drugs the patient excreted large amounts of fluid, but, despite this, his edema failed to improve.

Early in August his liver and spleen became quite tender and his icterus index rose to 159 units.

His general condition rapidly became critical, and on Aug. 6, 1943, he was conscious only for short periods of time; he expired on Aug. 7, 1943. The final clinical diagnosis was: massive aneurysmal dilatation, left ventricle, probably on the basis of myocardial infarction, with subsequent myocardial failure.

Autopsy Findings.—(For the sake of brevity only those findings considered to be significant are given.) The skin and sclerae were icteric, and there was pitting edema of the lower extremities.

A. Gross: Upon removal of the sternum and ribs, an extremely enlarged heart was encountered. The left border of the heart was in contact with the lateral thoracic wall. The enlargement had been to such an extent that approximately 85 per cent of the left pleural cavity was occupied by heart and tumor mass. There was also enlargement to the right so that the heart occupied approximately 35 per cent of the right pleural cavity.

The left lung was completely collapsed, had been markedly displaced posteriorly and superiorly, and was bound down by firm fibrous adhesions over the apical half. The right pleural cavity contained 750 c.c. of thin, yellowish-brown, cloudy fluid. The right lung was 75 per cent collapsed, and its surface, particularly in the lower half, was covered by yellowish-red fibrinous exudate.

The arch of the aorta was displaced superiorly.

The heart and lungs together weighed 2,960 grams, of which the lungs made up an estimated 450 grams (Fig. 6). The enlargement of the heart involved primarily the left ventricle. It extended about halfway around the heart by intrapericardial growth "encuirasse." The cavity of the left ventricle was considerably decreased in size, measuring 3.5 cm. from the aortic valve to apex. In the apex of the ventricle were two polypoid masses which projected into the cavity, further reducing its size. The cavity of the right ventricle was also somewhat decreased in its capacity, although less so than the left, and measured 4.5 cm. from the pulmonary valve to the apex. The chordae tendeneae were shortened, and the papillary muscles were somewhat hypertrophied. The hypertrophy of the right ventricular wall was particularly marked. This ventricle was also displaced upward, but was not invaded.

The endocardium throughout all chambers of the heart was smooth and glistening. There was no lesion of any of the valve leaflets. The valve rings were of their usual size, except for the aortic which had been mildly compressed by a large mass of tumor tissue, 4.5 by 2.2 cm., which was exactly similar to that which is described subsequently. This mass of tumor

Fig. 6.—Over-all appearance of the entire intrathoracic mass. (U. S. Army Medical Museum, Reg. No. 76862.)

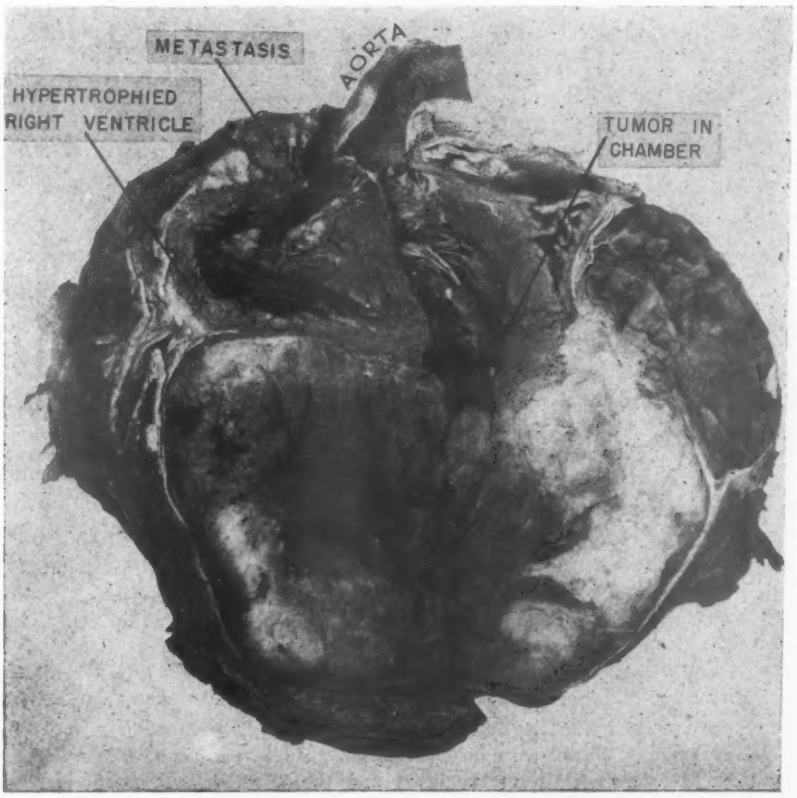


Fig. 7.—Tumor mass and heart opened to reveal the various features of the two. (U. S. Army Medical Museum Reg. No. 77304.)

tissue had also produced some compression of the superior vena cava as it entered the right auricle. One end of this mass lay upon but did not compress the pulmonary artery. This periaortic mass was entirely extra myocardial and extended upward from the auriculoventricular groove. It was in no way connected with the main tumor and was considered to be an intrapericardial metastasis.

Projecting from the apex of the heart was a large tumor mass which, from the inferior border of identifiable myocardium to the tip of the mass, measured 10 centimeters. This mass was composed of moderately firm, yellowish, tumor tissue, contained in which were several large areas of degeneration, the largest of which measured 4 cm. in diameter, and was centrally placed. Throughout the tumor mass were irregularly shaped strands of reddish-brown tissue which appeared to be degenerating myocardium. The line of demarcation between the tumor and the heart muscle was rather sharp (Fig. 7).

The tumor tissue itself occurred in ill-defined strands and whorls, some strands of which were paler and more dense than others. Upon sectioning, the tumor tissue swelled up and overhung the pericardium. Despite careful search, the exact site of origin of the mass could not be determined, although from its location it is safe to say that it probably was in or near the apex of the left ventricle.

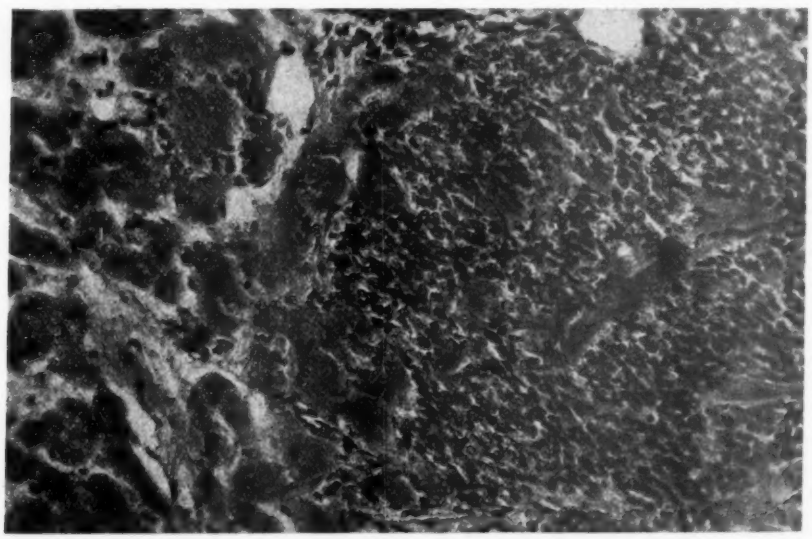


Fig. 8.—Photomicrograph showing encroachment on and isolation of myocardial cells by the neoplastic cells. (U. S. Army Medical Museum, Reg. No. 76432.) ×435.

The tumor mass had stretched the overlying visceral pericardium and was attached to it. This portion of the pericardium was somewhat thickened, averaging 0.15 centimeters. However, it could be dissected from the underlying tumor tissue without much difficulty. The pericardial space was completely obliterated, and the two layers of the pericardium could be separated only by sharp dissection. The parietal pericardium was thickened and averaged 0.2 centimeters. Neither layer of the pericardium showed any gross involvement by the tumor.

The peritoneal cavity contained 2,300 c.c. of thin, yellowish-brown, slightly cloudy fluid.

The duodenum contained three large ulcer craters, which were agonal in type.

Both the cystic and common bile ducts were occluded by enlarged, homogeneous appearing lymph nodes at points 1 cm. from the hepatic duct junction and 1.5 cm. distal to this junction.

The remaining abdominal organs revealed only a considerable degree of passive congestion.

Thorough examination of the brain failed to reveal any gross lesion.

B. Microscopic: The microscopic description for the purpose of this report is limited to the findings as they pertain to the heart and the tumor mass. Those sections of the myocardium taken away from the tumor mass revealed the muscle cells to be normal in their appearance although there were reactive changes in the myocardium with increased interstitial

tissue and a scattering of large mononuclear and other cells. The interstitial blood vessels were entirely normal.

The pericardium was moderately thickened and in some areas was slightly increased in its cellularity. Scattered diffusely through some areas of the pericardium were collections of lymphocytes.

The endocardium was not thickened in any area.

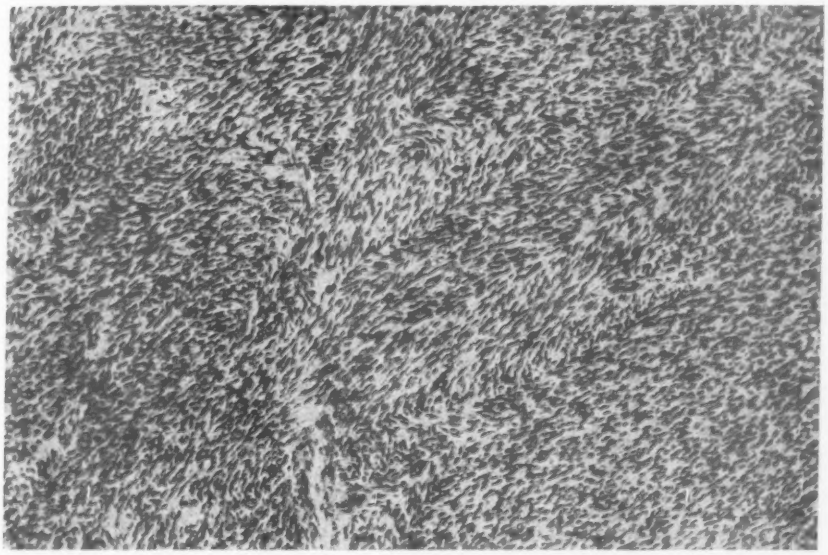


Fig. 9.—Photomicrograph revealing the cellular arrangement of the tumor. (U. S. Army Medical Museum. Reg. Nos. 77247, 77250.) ×165.

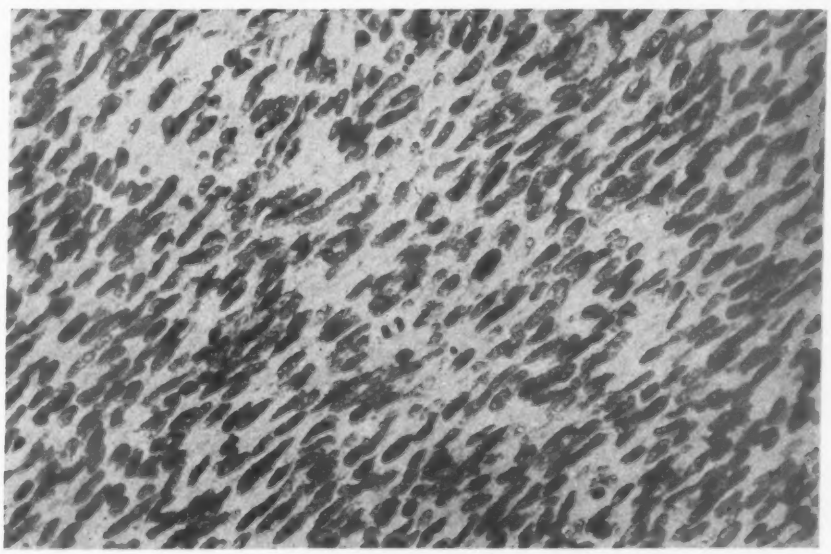


Fig. 10.—Photomicrograph revealing nuclear detail. Note arrangement of chromatin and mitotic figure. (U. S. Army Medical Museum, Reg. No. 77245.) ×640.

Sections taken from the line of juncture between the myocardium and the tumor mass revealed the latter to be encroaching upon the myocardial cells. Strands of the myocardium, as well as individual cells, were found deep within the tumor mass itself. These myocardial cells appeared as islands, having been isolated by the advancing tumor, and revealed varying degrees of degeneration (Fig. 8). In other areas there was a fairly sharp line of demarcation between the myocardium and tumor, and here a few strands of fibrous connective tissue formed a thin capsule between the two structures.

That portion of the tumor mass occurring closest to the myocardium was, by comparison with that elsewhere in the mass, much more cellular and of a higher degree of malignancy.

Sections from the bulk of the tumor mass were highly cellular; these cells occurred in whorls and bands projecting in all directions without any apparent attempt at reproduction of a specific architectural picture. The density of the tissue varied considerably from one area to the next. The individual cells of the tumor were not particularly large and were composed almost entirely of nuclear material. Cytoplasmic elements in some areas were indistinguishable; in others, however, varying amounts of cytoplasm could be made out. Where it could be made out, the cells were spindle shaped with pointed ends. No blue fibrils were found in the phosphotungstic acid hematoxylin preparations, although Wilder reticulum stains brought out some reticular fibers in relation to the cells. The nuclei were moderately chromatic; the chromatin was most dense around the periphery of the nucleus and accumulated throughout the remainder of this structure in dots of varying size with some arrangement in a vague linear fashion perpendicular to the long axis. Nucleoli were not common. There were occasionally as many as two mitotic figures per high power field (Figs. 9 and 10).

In many areas the tumor more or less suddenly differentiated itself from immature cells to a more mature type of cell which in all of its appearance and staining reactions was fibrous connective tissue. In these more mature areas the nuclei were more elongated, more compact, and the cytoplasm was more abundant. The area of degeneration described in the central portion of the tumor mass was found to be typical of the myxomatous type.

The polypoid tumor mass in the left ventricle was made up of tumor cells of the same type as previously described, which were collected largely in the base of the polyp itself. Towards the periphery of the polyp there was gradual differentiation through various stages to adult connective tissue which made up the enveloping capsule of the polyp itself. This differentiation was splendidly brought out by Masson's stains.

Sections of the mass which surrounded the base of the aorta were composed of neoplastic cells exactly similar in type to those already described.

The enlargement of the lymph nodes surrounding the biliary tract was found to be due to simple hyperplasia and early fibrosis, probably related to stasis.

COMMENT

As can be noted from the above protocol, the correct ante-mortem diagnosis was not made in this case. However, we wish to state that the presence of a cardiac tumor was mentioned as a possibility by many who observed this patient during the course of his illness. But no one thought the tumor possibility as being the most likely diagnosis.

The original electrocardiographic changes are those that may be seen in an infarction as well as in pericarditis without infarction. Because of the history of a choking sensation while the deceased was on a hike, the onset of which was sudden, followed by a pericardial friction rub and slight fever the next day, with associated electrocardiographic changes that were compatible with an early infarction, we concluded that the enlargement of the left ventricle seen on the roentgenogram of April 8, 1943, could easily be explained; namely, upon the basis of aneurysmal dilatation. The fluoroscopic examination performed on April 11, 1943, showed that the enlargement of the heart was limited to the apical portion of the left ventricle at which site weak pulsations were discerned.

The nonclearing of the electrocardiographic abnormalities over a period of several months (Figs. 11, 12, and 13) without clinical evidence of secondary infarctions was a bit disconcerting and failed to substantiate our impression of aneurysm incident to myocardial infarction. But then, later, the radiographic and kymographic findings of a boot-shaped appearing heart shadow and absent pulsations in the left ventricle gave us evidence that we thought was incontrovertible, and so we assumed that we were dealing with a rapidly stretching myomalacic left ventricle, which subsequently failed, terminating in the death of the patient.

The absence of paradoxical pulsations of the left ventricle upon fluoroscopic study did not alter our opinion of aneurysm, as we explained the lack of such pulsations upon the basis of a mural thrombus situated on the endocardial wall of the supposedly infarcted left ventricle. This thrombus was believed to be large enough to prevent any outward bulge during systole.

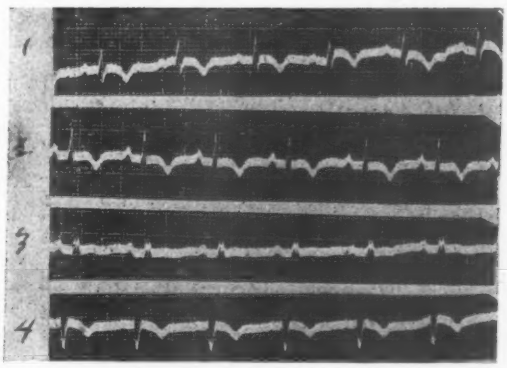


Fig. 11.—Electrocardiogram taken June 8, 1943, showing same degree of negativity of T waves in all leads. There is notching of R_3 and absent R_4. No RS-T elevation or depression but slight coving S-T_1 and S-T_2. Lead IV standard IVF.

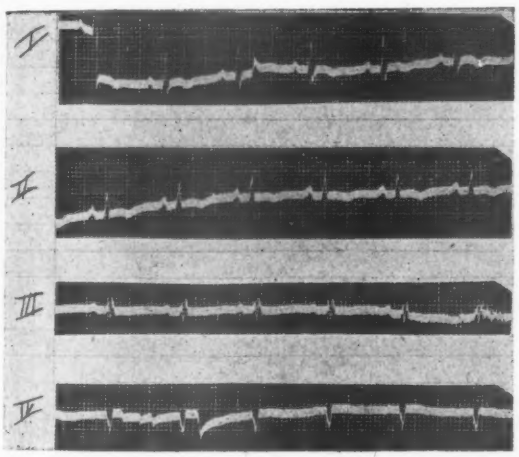


Fig. 12.

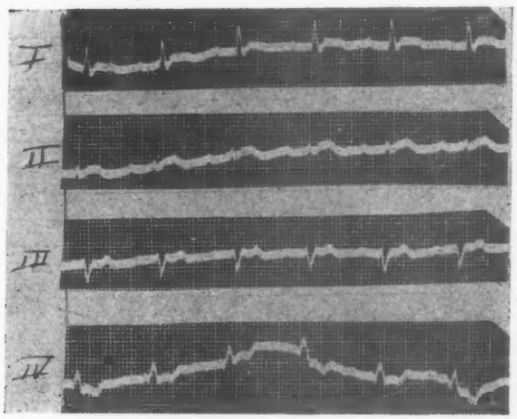


Fig. 13.

Fig. 12.—Electrocardiogram taken June 29, 1943, showing tendency toward left axis deviation. T_1 and T_2 are only slightly elevated now. T_3 and T_4 are isoelectric. R_4 is still absent. Still slight coving S-T_1 and S-T_2. Lead IV standard IVF.

Fig. 13.—Electrocardiogram obtained Aug. 7, 1943, showing low voltage QRS complexes all leads. T_1 and T_2 now are diphasic. T_3 is upright. T_4 is diphasic. R_4 is slurred. Slight elevation of S-T_1. Lead IV standard IVF.

However, in retrospect, we feel that there are certain findings that should have enabled us to differentially exclude aneurysm. In the first place, the presence of a friction rub for a period of ten days is unusual in a case of simple single infarction. Then, too, there was no blood pressure drop as is often seen in infarction of the left ventricle. In addition, the electrocardiographic changes were not typical of infarction in that originally all T waves were inverted with never any elevation or depression of the S-T segments, only slight coving. Later there was seen some notching of the QRS components which, in the absence of such notching during the two or more months following the onset of the supposed infarction, would point toward progressive myocardial pathology of some

type. In the absence of clinical or other laboratory evidence to support secondary infarction to account for the progressive nature of the electrocardiographic findings, the diagnosis of a tumor should have been more strongly entertained. Furthermore, the rapid enlargement of the heart should have aroused our suspicion more than it did, in favoring a diagnosis of tumor. This latter observation coupled with the relatively rapid course favored a tumor diagnosis rather than one of aneurysmal dilatation.

The autopsy findings are remarkable because of the single site of location of the tumor with only a single intrapericardial metastasis. Despite careful gross and microscopic examination of all tissues no evidence of distant metastases of any type could be discovered. This is felt to be significant because clinically the exitus was mechanical in type rather than due to late stages of malignancy. The microscopic examination, as noted, revealed a spindle-cell type of growth.

From the various staining procedures carried out, two main possibilities present themselves, namely fibrosarcoma and leiomyosarcoma; the latter is comparable to the rare pleural tumors.

The exact site of origin of the tumor cannot be postulated exactly, either from a gross or a microscopic standpoint. We are of the opinion that it started in or near the apex of the left ventricle and perhaps the pericardium. The occurrence of an isolated tumor mass at the base of the heart in the area of the ring of the aortic valve is interesting. As noted in the description, this mass had absolutely no connection with the main tumor mass, and it is felt that this represents an area of metastasis to the heart itself. The possibility of simultaneous origin of the two masses is considered but discarded because of insufficient evidence upon which to base such a conclusion.

Taking all of the gross and microscopic features into account, it is concluded that this is a leiomyosarcoma, while an alternative choice of fibrosarcoma is also suggested.

PRIMARY ALVEOLAR CELL CARCINOMA OF THE LUNG WITH PULMONARY ARTERY SCLEROSIS AND RIGHT HEART FAILURE

Case Report

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THE coexistence of pulmonary neoplasms and pulmonary arteriosclerosis is rare. In a recent review of the pathology of the vessels of the pulmonary circulation Brenner[1] found but one such case in his series of one hundred patients and gathered four others from the literature. We are reporting an additional case which is interesting because of the association of advanced atherosclerosis of the pulmonary arteries and cor pulmonale with a diffuse alveolar cell carcinoma of the right lung in a young woman.

REPORT OF A CASE

R. W., a 20-year-old college girl, was told she had a "spot" on her right lung in 1939 after a routine roentgenogram of her chest had been made. The heart silhouette at that time was normal. Because of her apparent good health the finding was disregarded. Two tuberculin tests were negative.

During June, 1940, she complained of pain in the right side of the chest which was diagnosed as right basal pneumonia with pleurisy. A moderately productive cough without hemoptysis appeared and persisted for three weeks. The cough and pain in the right side then became less intense and was present when she was admitted to the hospital on Feb. 2, 1941. She stated that she had lost 4 pounds in the month before admission.

She was in good physical condition when first examined. Percussion dullness and exaggerated breath sounds were present over the right lung base. The heart sounds were regular, and aside from accentuation of the second pulmonic sound no changes were apparent. The liver edge could not be palpated.

A chest teleroentgenogram revealed a uniform opacity extending obliquely from the right lung root to the diaphragm obscuring the right heart border. The main trunk of the pulmonary artery was prominent. At first the possibility of a congenital heart lesion was considered, but a review of the film taken in 1939 made it clear that the pulmonary artery prominence had developed since that time.

The blood Kline reaction was normal. A blood count revealed her hemoglobin to be 107 per cent, with 5.5 million red cells, 13,300 white cells, and a normal differential count.

Bronchoscopic examination revealed slight narrowing of her right lower bronchus with chronic inflammatory changes. A biopsy was reported as chronic inflammatory tissue. Iodized oil bronchography showed slight bronchiectatic changes in the lower lobe bronchi. The lumen of the trachea and main bronchi was normal.

On Nov. 25, 1941, she was readmitted because of fever, chills, and a hard cough productive of thick, green, mucoid sputum. She appeared malnourished, her lips were cyanotic, and her fingers were clubbed. There was dyspnea on slight exertion, and edema was present over the sacrum and ankles. A flat percussion note, increased tactile fremitus, and bronchial breathing were present over the right base posteriorly. Many moist and dry fine râles were heard over the entire chest. The heart rhythm was regular, and the sounds were not unusual except for an accentuated second pulmonic sound. The liver could now be felt 4 finger-breadths below the costal margin.

Teleroentgenographic examination of the chest showed the right lung opacity to be more extensive than it was previously, obliterating the right costophrenic sinus. Her heart was

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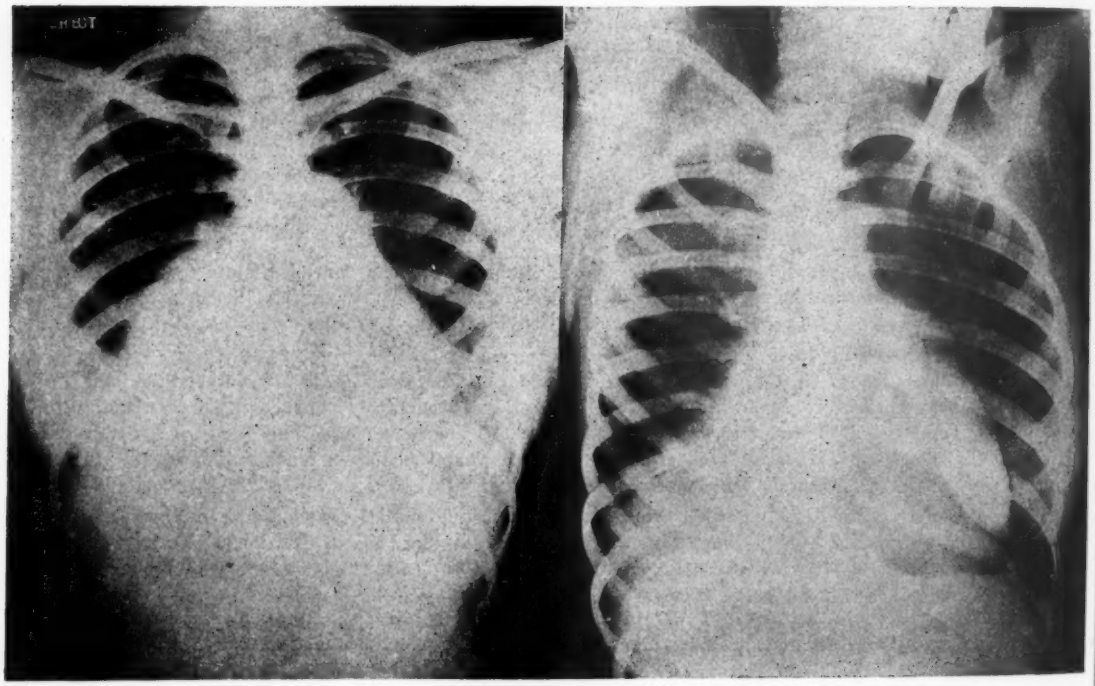
displaced toward the left, and there was marked prominence and increased amplitude of pulsation of the main trunk of the pulmonary artery.

Bronchoscopic examination again revealed the chronic inflammatory changes in the right lower bronchus. Electrocardiographic examination showed right axis deviation and changes in the main ventricular complexes due to myocardial changes. Her venous pressure was 130 mm. of water, the saccharin circulation time was 25.5 seconds, and the ether circulation time was 16.5 seconds.

The patient grew progressively worse during the next few weeks. Cyanosis increased markedly, and the dyspnea and orthopnea became more pronounced. About 50 c.c. of mucopurulent sputum were expectorated daily. The peripheral edema was not relieved by vigorous attempts to induce diuresis.

An exploratory thoracotomy for a possible lung tumor, performed five weeks after admission, revealed an inoperable mass involving the right lower lobe and extending into the upper lobe. The patient expired eighteen hours after operation in advanced heart failure.



A. *B.*

Fig. 1.—*A*, Teleroentgenogram showing opacity in right lung base and paracardiac region. The heart is shifted toward the left. The main trunk of the pulmonary artery is prominent. *B*, Right anterior oblique projection showing dilatation of the main trunk of the pulmonary artery and prominence of the conus of the right ventricle.

The following are the significant observations made at post-mortem examination. Her right lung weighed 780 grams, and her left lung weighed 240 grams. The right lung was firm, rubbery in consistency throughout except at its apex, and presented deep red-grey surfaces on cut section. At first glance the possibility of a pneumonic consolidation was considered. No necrotic foci were seen. The trachea and main bronchi were normal throughout. The left lung revealed a few circumscribed nodules in the lower lobe which proved to be metastatic.

The main trunk of the pulmonary artery presented numerous grey-yellow atheromatous plaques which rendered the vessel almost rigid. The atherosclerosis extended into the lesser branches of the pulmonary arteries in both lungs so that they projected well above the cut surfaces.

The heart weighed 315 grams. The right ventricle was markedly thickened, measuring 1.2 centimeters. The left ventricle was 1.4 cm. thick. The coronary arteries were patent and contained occasional small yellow atheromatous plaques. The myocardium and valves were normal.

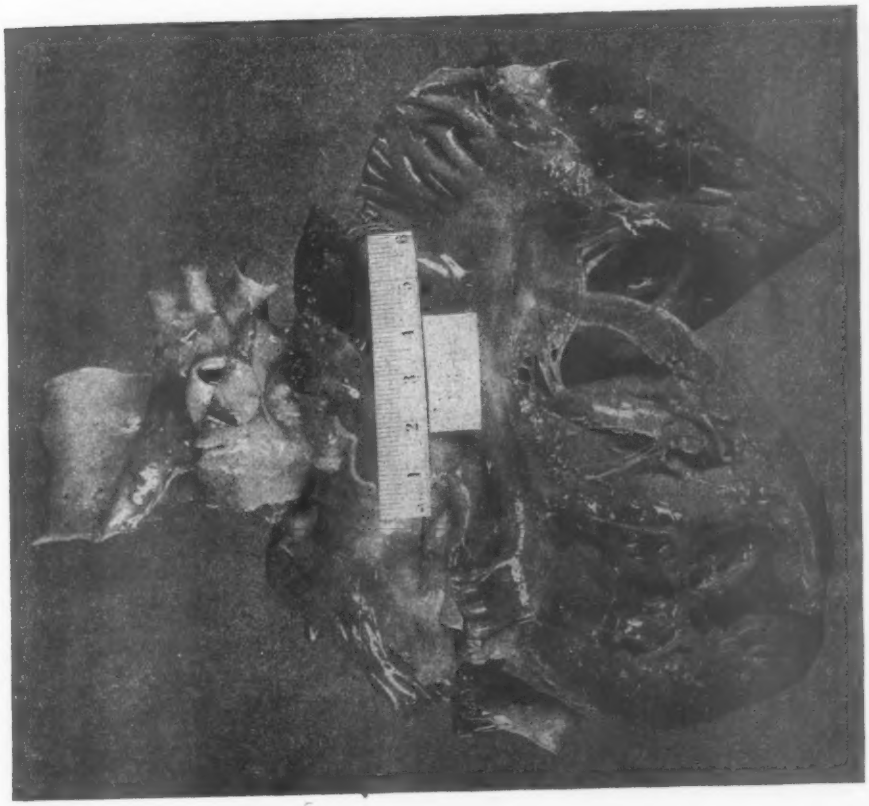


Fig. 3.—Photograph of the heart showing hypertrophy of the right ventricle.

Fig. 2.—Photograph of the right lung showing diffuse carcinoma and pulmonary artery sclerosis.

On microscopic examination the right lung parenchyma was diffusely infiltrated with tumor cells which filled the alveoli and extended into the bronchi and bronchioles. The stroma of the tumor was made up of the alveolar walls. The alveolar structures which remained in the diffuse sheet of tumor cells existed as incomplete single layers of large cuboidal cells with large hyperchromatic nuclei. The tumor cells were large, either round or polygonal in shape, and had large or vesicular deeply-staining nuclei. Mitotic figures were rare.

There was marked thickening of the walls of the arteries and arterioles with intimal proliferation which resulted in considerable narrowing of the lumina of the smaller vessels. No such changes were noted in the smaller vessels of the kidneys, liver, or heart.

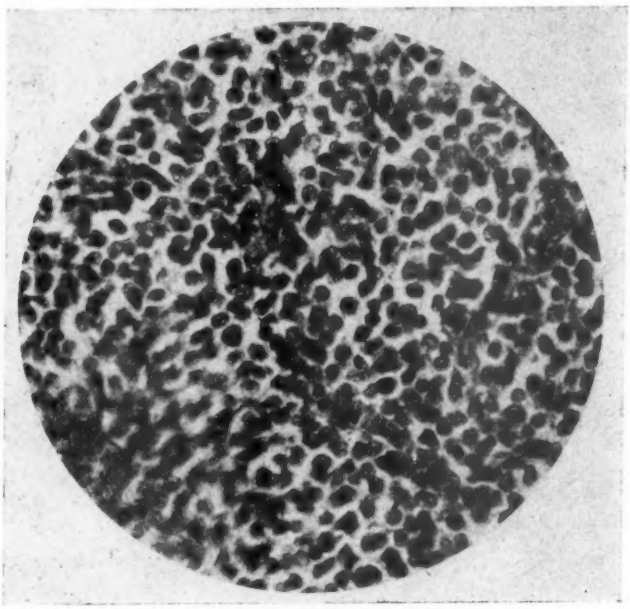


Fig. 4.—Photomicrograph showing the tumor cells (hematoxylin and eosin stain; magnification, ×400).

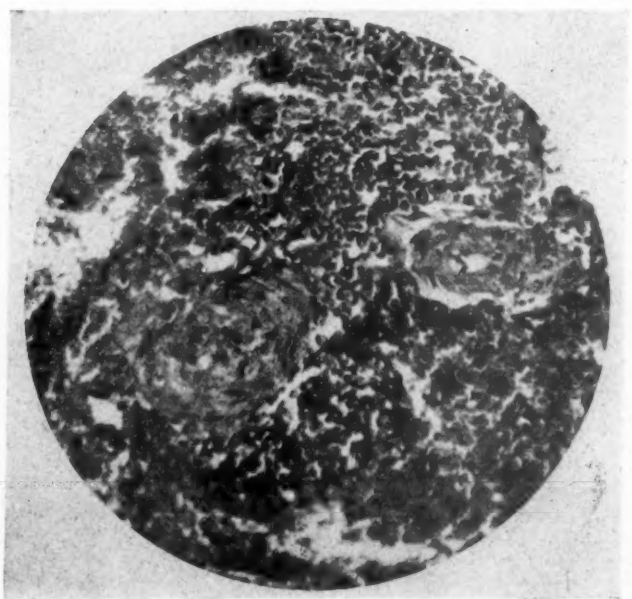


Fig. 5.—Photomicrograph showing the thick-walled vessels with narrowed lumina (hematoxylin and eosin stain; magnification, ×150).

COMMENT

Pulmonary arteriosclerosis is usually divided into "primary" and "secondary" groups. The former refers to those for which no cause for pulmonary hypertension can be found and is usually accompanied by right ventricular hypertrophy. Cases sometimes referred to as senile in origin fall into this group even though there is neither right ventricular hypertrophy nor any obvious cause for the pulmonary hypertension.

Secondary pulmonary arteriosclerosis is the designation applied to the larger group in whom some obvious pulmonary or cardiac cause for the increased pulmonary arterial pressure exists. Among these are heart disease, particularly mitral stenosis, chronic heart failure, and chronic lung conditions such as bronchiectasis, emphysema, tuberculosis, lung abscess, and extraluminal compression of the pulmonary artery.

In 1942, Neuberger and Geever[2] reported the pathologic findings in twenty-five cases of alveolar cell carcinoma of the lung gathered from the available literature. In none of these was there any mention of pulmonary arteriosclerosis. Brenner was unable to ascribe any relationship between the lung tumor and pulmonary arteriosclerosis in the five cases he mentioned.

The ultimate cause of the pulmonary hypertension could not be ascertained in our patient. It might be more than coincidental that the pulmonary arteriosclerosis and the alveolar cell carcinoma of the right lung were present together. The fact that the pulmonary artery dilatation and the cor pulmonale appeared after the first x-ray examination of the chest in 1939 suggests that perhaps some relationship may have existed between the pulmonary artery sclerosis and the tumor.

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Abstracts and Reviews

Selected Abstracts

Rosenblueth, P. A., and Ramos, J. G.: The Interpretation of the Electrogram of the Cardiac Ventricle. Arch. Inst. Cardiol. Mex. 14: 232, 1945.

The electric phenomena of the cardiac ventricles of cats and dogs were recorded by means of a cathode-ray oscillograph and the following observations were made.

When the leads are applied directly to two intact regions of the muscle, a typical diphasic electrogram is obtained. If an extensive injury (ligature or burn) is made between the leads, the records are not modified, although the response recorded from the injury to either of these two intact regions tested originally are typically monophasic.

The existence of an injured region can only be appreciated in records taken from a direct to a distant lead if the direct lead is in contact with the damaged tissue. If, instead of being applied directly, the near electrode is placed on a layer of cotton moistened with Ringer's solution which covers the heart, so that the lead becomes diffuse and makes contact with both injured and intact tissue, then the existence of an injury can be appreciated in the records even when the electrode is moved over a relatively large area in front of the heart.

The polarization with direct current of either of the two lead-off regions results in marked changes of the diphasic electrograms. Applications of direct current to other regions of the heart, including the zone intermediate to the leads, do not modify the electrograms. Similarly, the monophasic records are strikingly modified when the live lead-off region is polarized anodally or cathodally, but are unchanged by the application of direct current to the intermediate zones or to the injured region.

From these data the following inferences are drawn. (a) The only regions in the ventricle that contribute significantly to the electrograms obtained with leads applied on the surface are those in direct contact with the leads; the electrical phenomena which occur in other regions, including those intermediate to the leads, contribute only minimally or do not contribute to the electrograms. (b) There are no potential changes at an injured region concomitant with the activity of the heart. (c) The monophasic electrograms, therefore, show only the potential changes which take place at the intact region which is in contact with the corresponding electrode; they may be designated as monotopic; the diphasic electrograms are ditopic since they correspond to the algebraic sum of the two monotopic responses. (d) When applications of direct current to the injured region do not modify the monophasic electrograms it may be concluded that the injury is complete for the purpose of the record, and it may be concluded, therefore, that the electrograms are strictly monotopic; these strictly monotopic records are not simple but complex, they exhibit several components which differ in amplitude, polarity, and time course. (e) The existence of a cardiac injury may be detected in the human electrocardiogram because the distant electrodes are prolonged by the conducting media of the organism and the real leads are diffuse and come in contact with the injury.

AUTHORS.

Alexander, R. S.: The Effects of Blood Flow and Anoxia on Spinal Cardiovascular Centers. Am. J. Physiol. 143: 698, 1945.

By employing the activity in the inferior cardiac nerve of the cat as a direct index of the activity in the sympathetic outflow to the cardiovascular system, the following conclusions have been reached:

After removal of all possible sources of reflex inhibition, a rise in thoracic blood pressure produced by injections of adrenalin or pitressin or by sudden occlusion of the abdominal aorta still serves to inhibit the tonic activity in the thoracic sympathetic outflow to the cardiovascular system.

The tonic activity arising within the spinal cardiovascular centers of deafferent spinal preparations is sensitive to changes in oxygen tension. This activity is depressed by hyperventilation or ventilation with a mixture of 90 per cent oxygen and 10 per cent carbon dioxide, and stimulated by asphyxiation or ventilation with pure nitrogen.

In the deafferent spinal preparation, a rise in blood pressure inhibits sympathetic activity by increasing the flow of blood to the spinal cord. This increases the supply of oxygen to the spinal cardiovascular centers and thus depresses their activity.

It is suggested that the oxygen tension in the spinal cord of the normal animal may contribute to the excitatory state of the spinal cardiovascular centers, and thereby reinforce the buffer reflexes which are integrated at higher levels of the nervous system.

AUTHOR.

Duomarco, J., Recrate, P., and Rimini, R.: Influence of Abdominal and Thoracic Pressure Upon the Venous Return in the Inferior Vena Cava. Rev. argent. de cardiol. **11**: 286, 1945.

An artificial experimental model was devised in which the physical conditions which determine the venous return in the inferior vena cava were studied.

In the case of the inferior vena cava there is a phenomenon of venous collapse which makes it impossible for the variations of thoracic and abdominal pressure to influence directly the venous return.

The thoraco-abdominal pressure difference protects the abdominal venous system from any easy stagnation.

The pressure variations due to respiration may cooperate in the venous return only in certain conditions in which the inferior vena cava is distended.

AUTHORS.

Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization. Normal Values With Observations on the Effect of Anxiety and Tilting. J. Clin. Investigation **24**: 326, 1945.

Studies on the circulation were performed in twenty-two normal subjects in the basal state. Samples of mixed venous blood and measurements of the atrial pressure were obtained by inserting a catheter through the antecubital vein into the right atrium. The femoral arterial pressure was recorded optically by the method of Hamilton.

Nineteen experiments were carried out on eighteen subjects in whom the pulse rate was not above 82 beats per minute and in whom the metabolic rate did not exceed plus 10. The arteriovenous oxygen difference varied from 3.1 to 6.1 with an average of 4 volumes per cent. The cardiac index (liters per minute per square meter) ranged from 2.3 to 4.1, with an average of 3.3. The atrial pressure ranged from 0 to 85, with an average of 31 mm. of water.

Seven experiments were performed on five normal subjects in whom either the pulse rate exceeded 82 or the metabolic rate exceeded plus 10. These findings were interpreted as evidence of anxiety. The average arteriovenous oxygen difference was 3.1 volumes per cent. The cardiac index averaged 5.5, and the atrial pressure averaged 29 mm. of water. The increase in cardiac output was out of proportion to the increase in oxygen consumption. The rise in cardiac output occurred without any measurable change in atrial pressure.

When the subject was tilted to an angle of 70 degrees, the arteriovenous oxygen difference rose, and the cardiac output decreased. The average decrease in the cardiac index, when the subject was tilted, amounted to 23 per cent.

AUTHORS.

Neubauer, C.: Auricular Fibrillation and Auricular Flutter in Diphtheria. Brit. Heart J. **7**: 59, 1945.

On clinical and bacteriologic grounds, the case was one of faucial diphtheria. Hemolytic streptococci are not uncommonly found in diphtheritic throat lesions caused by gravis strain, and in the case under discussion the presence of hemolytic streptococci, in addition to the development of a rash and strawberry tongue as described above, indicates beyond doubt a double infection. The persistent tachycardia and the diminished intensity of the first apical sound, the lowered blood pressure, and the increased blood sedimentation rate were clinical manifestations of a myocarditis. Auricular fibrillation, detected clinically and cardiograph-

ically three days later, confirmed the presence of myocarditis; it persisted for two days in spite of digitalis therapy and ultimately changed to auricular flutter. Anatomic and histologic findings at autopsy revealed an acute myocarditis with formation of ante-mortem mural thrombi.

Here, then, is an example of auricular fibrillation and auricular flutter developing as terminal events in the course of an extremely acute myocarditis.

AUTHOR.

Cookson, H.: Heart Block and the Simulation of Bundle Block in Diphtheria. Brit. Heart J. 7: 63, 1945.

Clinical and cardiographic findings are given of eight cases showing conduction changes among a series of eighty-three patients with diphtheria. Of four with latent block, a prolonged P-R interval has persisted in one for five months. Bundle branch block was observed in four unimmunized children, aged 12 years or less, and all died; complete block was recorded in one of these four. In two others bizarre ventricular complexes were found in association with a passive ectopic rhythm; at first sight these suggest a bundle branch lesion, but like the short P-R wide QRS syndrome, which seems a related condition, these changes do not appear to have any prognostic significance.

AUTHOR.

Pearson, R. S. B.: Sinus Bradycardia With Cardiac Asystole. Brit. Heart J. 7: 85, 1945.

A case of persistent sinus bradycardia with syncopal attacks due to cardiac standstill is described.

Evidence is given for believing that this is not vagal in origin but due to hypo-excitability of the pacemaker.

AUTHOR.

Costero, and Fuertes, G. A.: Frequency of Congenital Anatomic Lesions of the Heart in the City of Mexico. Arch. Inst. Cardiol. Mex. 14: 275, 1945.

In 1,000 consecutive autopsies with a complete pathologic study recorded in the Service of Pathology of the General Hospital of Mexico and carried out for Sept. 11, 1937, to Jan. 19, 1941, the frequency of congenital anatomic lesions of the heart and of the large vessels has been investigated with the following results:

1. Fenestration of the sigmoid valves was found in 253 cases. In 107 of them the lesion was of the pulmonary sigmoid; in 67, of the aortic sigmoid; and in 79, of the valves of both arteries. Of these cases 48 (18.97 per cent) coincided with other congenital abnormalities in the organism.
2. The foramen of Botal was incompletely closed in 179 cases, of which 80 (44.69 per cent) coincided with other congenital malformations.
3. The coronary arteries were abnormal in 36 cases; in 14 there were accessory coronaries; in eight there was duplicity in the opening of one of the coronaries; in two there were multiple openings; and in 12 the opening was displaced.

The following abnormalities were found only once.

4. Bivalve sigmoid, which coincided with other extracardiac congenital malformations.
5. Incomplete interauricular septum, coinciding also with other malformations.
6. Bifurcation of the apex, associated with fenestration of the sigmoid.
7. Dilatation of coronary sinus.

In 90 of the cases tabulated there were two simultaneous lesions, and, in five of them, there were three simultaneous congenital lesions of the cardiovascular system.

AUTHORS.

Grolnick, M., and Loewe, L.: Immunologic Studies in Patients With Subacute Bacterial Endocarditis Treated by Combined Penicillin-Heparin Method. J. Lab. & Clin. Med. 30: 559, 1945.

Twenty-seven patients receiving intensive and prolonged treatment with penicillin failed to develop any positive skin or ophthalmic reactions to a solution of penicillin containing 10,000 units per cubic centimeter. These patients did not develop any positive skin reactions to the source of this product, the mold *Penicillium notatum*.

From the present study penicillin would appear to be a very poor sensitizing agent.

AUTHORS.

Katz, L. N., Wise, W., and Jochim, K.: The Control of the Coronary Flow in the Denervated Isolated Heart and Heart-Lung Preparation of the Dog. Am. J. Physiol. 143: 479, 1945.

Coronary flow was studied in isolated heart and heart-lung preparations of dogs by examination and analysis of graphs correlating one or more factors with coronary flow in the control period at the start of each of seventy-nine experiments, and by data obtained in individual experiments following alteration of the various factors controlling the dynamics of the preparation.

In the graphs, coronary flow at the beginning of the experiments was found to vary with heart weight, but not with venous or aortic pressure levels. On the other hand, there was striking correlation of cardiac output (measured as pulmonary flow) with coronary flow, index of reciprocal of coronary resistance ($\frac{\text{coronary flow}}{\text{aortic pressure}}$), coronary flow per gram heart weight and $\frac{\text{coronary flow}}{\text{aortic pressure}}$ per gram heart weight. Correlations of work of the heart were similar to those of pulmonary flow since in our preparations the latter is the main variable in calculation of cardiac work. Coronary flow was found to be independent of aortic flow and of arterial oxygen level (of the range in our experiments) but coronary flow per gram heart weight tended to increase with increase of temperature or heart rate. The pressure drop between the aorta and right auricle in the heart-lung preparation correlated with aortic flow but not with coronary flow, indicating great variation in cross section of the coronary bed from preparation to preparation.

Examination of the course of individual experiments explained the above correlations and lack of correlations. They showed that the two most important mechanical factors influencing coronary flow in the isolated heart and heart-lung preparations, and presumably in the intact circulation, are cardiac output and systemic peripheral resistance—apart from spontaneous changes in coronary resistance which tend to occur during the course of the experiments. Thus, both increase in minute cardiac output and increase in extracoronary vascular resistance increase coronary flow.

These two factors act automatically and mechanically, without involving nerve reflexes or humoral mechanisms to bring about their effect. Their importance has hitherto not been properly appreciated.

Aortic pressure, which has an important influence on coronary flow in artificial preparations in which the coronary circuit is dissociated from the systemic circuit, does not play as important a part in the intact circulation. In the intact circulation, changes in aortic pressure are usually coincidental, secondary to change in cardiac output, systemic peripheral resistance, or both. The aortic pressure change tends to be minimized as a result of lessening of the change in total peripheral resistance by the alteration in coronary resistance brought about in turn by the passive alteration in the diameter of the coronary vessels. Change in coronary flow due to the predominant influence of one or both of the two factors mentioned above may occur in the absence of, or with similar or opposite, change in aortic pressure.

The degree of cardiac extravascular coronary compression is not as marked an influence as these other two factors, and its effect is obscured. Similarly the effect of cardiac output and peripheral resistance may mask or reverse the influence of nerve reflexes, drugs, and humoral substance on coronary caliber and coronary blood flow.

In experiments in which heart rate was deliberately altered there was no predictability in the change in coronary flow, since coronary flow changes occurred as the result of change in cardiac output or peripheral resistance, and no effect of heart rate per se could be distinguished.

The lack of relationship of coronary flow to aortic flow in the control periods of different preparations compared to the correlation of coronary flow with pulmonary flow, and the similar variability of aortic flow with respect to both coronary flow and pulmonary flow during the course of individual experiments, shows the fallacy in assuming, as some have done, that aortic flow below the mouths of the coronaries is an accurate index of either coronary flow, total cardiac output, cardiac work, or stroke volume. AUTHORS.

Katz, L. N., Wise, W., and Jochim, K.: The Dynamics of the Non-Failure Period of the Isolated Heart and Heart-Lung Preparation. Am. J. Physiol. 143: 495, 1945.

In order to determine how many of the changes occurring in the course of heart failure are attributable directly to the loss of power of the heart, and how many represent spontaneous change or changes induced by manipulation, the constancy and interrelation of the

various pressures and flows in the period of little or no failure in thirteen isolated hearts and twenty-five heart-lung preparations are considered.

Improvement of the heart was frequently seen and manifested by a fall in venous pressure with constant cardiac output and work, or by an increase in cardiac output without rise in venous pressure. Improvement of the heart occurred early and apparently represented recovery from the initial manipulations in setting up the preparation; it also occurred later and in these cases, as in others, a common factor apparently was improvement in coronary flow.

In the course of a number of experiments a spontaneous decrease in coronary resistance led to increase in coronary flow, and, since the total peripheral resistance tended to decline, aortic pressure tended to fall. Usually peripheral resistance was adjusted to keep up aortic pressure. In a number of experiments the aortic pressure did not fall even though the systemic peripheral resistance was not adjusted. The probable explanation for this is discussed. The effects of spontaneous coronary dilatation upon the pulmonary arterial and the venous pressures varied and were actually determined by coincidental adjustments or changes. The spontaneous changes in coronary flow could not be correlated with variations in arterial oxygen content; apparently anoxemia of a degree sufficient to affect coronary flow was not encountered in these experiments.

Almost all the spontaneous changes in heart rate were related to temperature change and averaged about 10 beats per minute per degree centigrade. No correlation between heart rate and right venous pressure levels could be established.

Deliberate changes in cardiac output were accompanied by a like change in one or both venous pressures. In the heart-lung preparation the right venous pressure change was greater and more frequent than left. In the isolated heart preparation the left venous pressure rise was more frequent and greater than the right. Aortic pressure tended to rise but not in all cases. The cause for these changes is discussed.

When changes in the artificial systemic resistance did not change the aortic pressure, change in the other pressures was usually minimal or absent. When the aortic pressure was elevated by this procedure left venous pressure usually rose. A rise was seen less frequently and to a lesser extent in the pulmonary arterial and right venous pressures. Contrary effects of the increase in peripheral resistance operating downstream sometimes neutralized or reversed the pressure changes on the right side of the heart. Increase in artificial aortic resistance operated to raise the pressures upstream and lower them downstream.

Alteration in the pulmonary resistance in the isolated heart preparation caused changes in the same direction in pulmonary arterial pressure, right venous pressure, and, usually, aortic pressure.

Apart from the effect of secondary adjustments when the heart rate was changed, increase or decrease in heart rate beyond the optimum for adequate filling decreased the cardiac output. Arterial pressures tended to fall and venous pressure to rise, and the rise in venous pressures was accentuated by adjustments in peripheral resistances to maintain the arterial pressures.

The development of pulmonary edema, but not the plugging up of minor vessels by thrombi (both rare phenomena), increased the pulmonary resistance, increased the pulmonary arterial to venous pressure drop, and led to an increase in right venous pressure.

Spontaneous decreases in pulmonary resistance in the heart-lung, usually associated with simultaneous decrease in coronary resistance, decreased the pressure drop from pulmonary artery to vein and were usually reflected also in a fall in right venous pressure. Increase in the pulmonary flow by distending the lung blood vessels in the heart-lung tended to lessen the expected increase in the pressure drop between the pulmonary artery and veins.

AUTHORS.

Nylin, G.: Blood Volume Determinations With Radioactive Phosphorus. Brit. Heart J. 7: 81, 1945.

By the application of a new method worked out by Hevesy and his co-workers, employing blood corpuscles labeled with radioactive phosphorus, the circulating blood volume has been determined on both normal persons and cardiac patients with and without failure. A prerequisite for the determination of the circulating blood volume is that the dilution curves can be established and thereby the time when equilibrium appears can be determined.

In this work the results in each case are based on the mean values of a number of determinations. The mean value for the amount of the circulating blood corpuscles in normal cases was found to be 1,850 c.c., 1,998 grains, or 33.4 Gm. per kilogram of body weight.

The mean value of the compensated cases is in agreement with the normal values at 1,795 c.c., 1,939 grains, and 31.8 Gm. per kilogram of body weight. The total blood volume in the normal cases is 73.5 c.c. per kilogram of body weight, and in the compensated cases 71.8 cubic centimeters. Two cases of heart failure—and particularly one of them—show a considerable increase in both the amount of blood corpuscles and the circulating blood volume. The other case has been followed with repeated determinations after all signs of failure had disappeared. A great decrease in the circulating blood volume of no less than 28 per cent took place simultaneously with the appearance of the interesting phenomenon that the amount of red blood corpuscles also decreased by 18 per cent.

AUTHOR.

Wiggers, C. J.: The Failure of Transfusions in Irreversible Hemorrhagic Shock. Am. J. Physiol. **144**: 91, 1945.

If reduction in circulating volume and in venous return, due either to exemia or to failure of a venopressor mechanism, are dominant factors in the circulatory failure which follows substantial infusions of adequate solutions, it may be anticipated that effective central venous pressures are reduced, as they are after large hemorrhages. It has been found that this is true in only eighteen out of forty-eight dogs submitted to our standardized technique for production of hemorrhagic shock.

The additional observations that effective venous pressures immediately after death from hemorrhagic shock are essentially within normal ranges and that the static circulatory equilibrium produced by prolonged vagal inhibition of the heart is also essentially normal fail to support the views that capillary transudation, pooling of blood in the vascular system, or failure of any venopressor mechanism represent the essential irreversibility factor in the majority of our animals.

The results strongly suggest that failure of transfusions in shock are not necessarily due to unsuitability of solutions used nor chiefly to loss of plasma or solutions through damaged capillaries or failure of a venopressor force, but, frequently at least, are attributable to myocardial depression, i.e., to a reduced reaction to equivalent venous filling pressures.

AUTHOR.

Bourne, G.: Ligature of Patent Ductus Arteriosus. Brit. Heart J. **7**: 91, 1945.

In infected cases of patent ductus arteriosus, successful ligature of the ductus brings about a lasting cure.

In noninfected cases it may be most successful even at the stage when heart failure is developing.

AUTHOR.

East, T.: Ligation of the Patent Ductus Arteriosus. Brit. Heart J. **7**: 95, 1945.

Ligation of the patent ductus arteriosus has been performed in thirteen cases. No anxiety arose in any case following operation. One patient, infected before operation, died later. One other patient died of septicemia which started after nine days' normal convalescence. It may possibly have arisen as a result of the operation, but there was no direct evidence of this.

The conclusion is that ligation is a good method of treatment in any patient with patent ductus arteriosus; the sooner after the sixth year, the better.

AUTHOR.

Moses, C.: The Effect of Digitalis, Epinephrine, and Surgery on the Response to Heparin. J. Lab. & Clin. Med. **30**: 603, 1945.

A study of the response of individuals to the intravenous administration of 0.15 mg. of heparin per kilogram of body weight is presented.

No significant decrease in heparin tolerance was obtained after the administration of digitalis or epinephrine or after major surgery.

AUTHOR.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

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